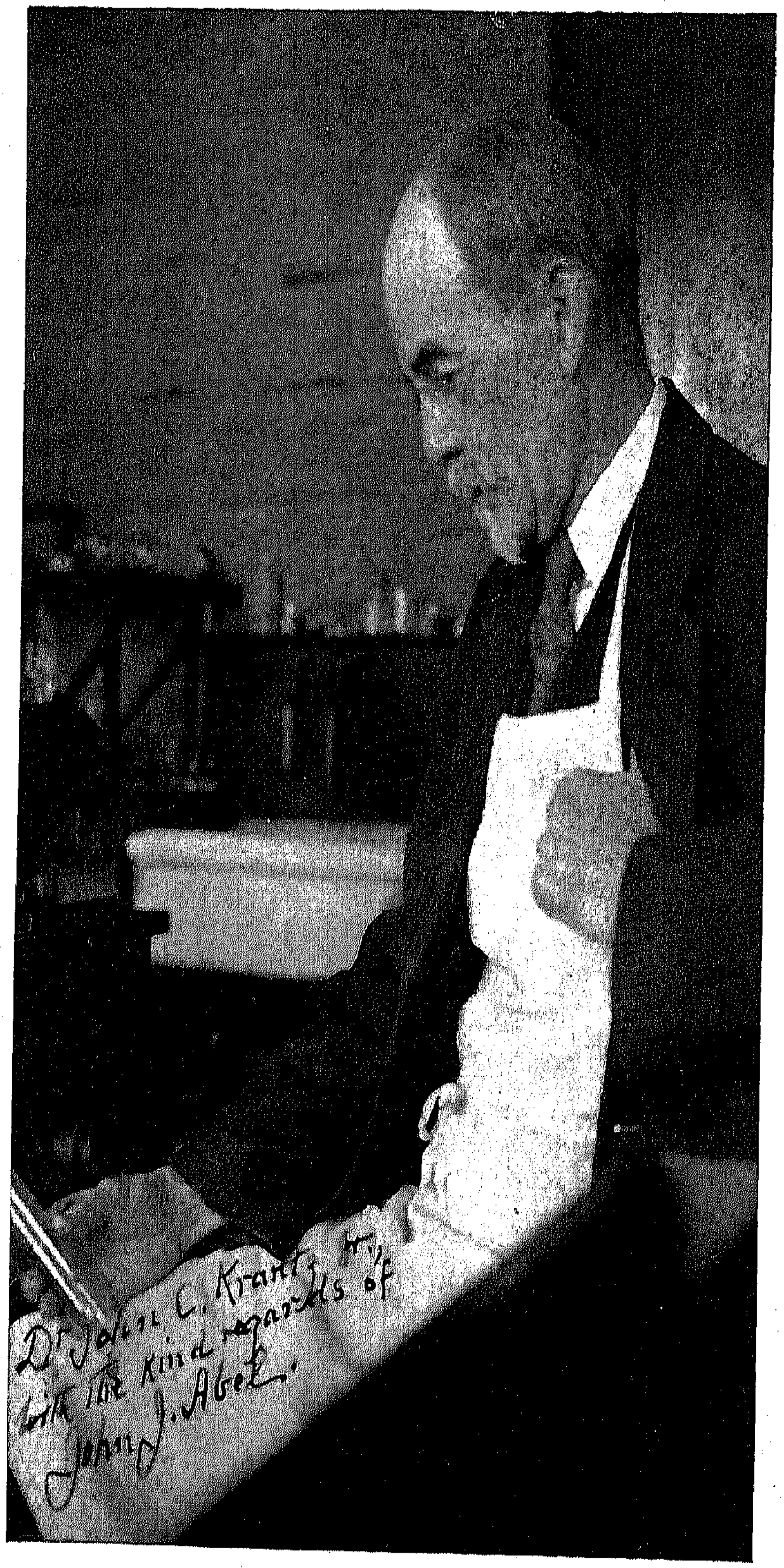
# THE PHARMACOLOGIC
# PRINCIPLES OF
# MEDICAL PRACTICE


Dr John C. Krantz, Jr,
with the kind regards of
John J. Abel.

JOHN JACOB ABEL
1857–1938
*The Dean of American Pharmacologists*

"This substance, as we now know, is an amino alcohol of a relatively simple constitution, characterized by the chemical name dihydroxymethylaminoethylol-benzene (epinephrine)."

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# THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE

## A TEXTBOOK ON PHARMACOLOGY AND THERAPEUTICS FOR MEDICAL STUDENTS, PHYSICIANS, AND THE MEMBERS OF THE PROFESSIONS ALLIED TO MEDICINE

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*Sixth Edition*

*Indian Edition* / 1965

*Second Reprint* / 1967

THE WILLIAMS & WILKINS COMPANY
BALTIMORE

SCIENTIFIC BOOK AGENCY
CALCUTTA

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Indian Edition Published 1965
Second Reprint 1967
SCIENTIFIC BOOK AGENCY
22 Kaja Woodmunt Street
Calcutta 1

Sales Area of Indian Edition

Japan, Taiwan, Okinawa, Vietnam, Cambodia,
Laos, Thailand, Malaysia, Burma, Indonesia,
Pakistan, India, Ceylon, Afghanistan, Hong Kong, Korea

Published by special arrangement with the original
publishers, The Williams & Wilkins Company,
Baltimore, Md. 21202 U.S.A.

This book has been published with the assistance of the
Joint Indian-American Standard Works Programme.

Price Rs. 20.00

Composed and Printed at the
WAVERLY PRESS, INC.
Baltimore, Md. 21202, U.S.A.

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# *Preface to the Sixth Edition*

The principal aim of the 6th edition of this treatise is the same as that established in the previous editions. It is expressed in the title. "Principles" embraces what to do and why; "practice" is how to do and when. We have retained essentially the same general arrangement of the subject matter, with certain minor modifications.

Several changes of considerable magnitude have been made. Each chapter is preceded by a topic outline indicating the major topics discussed, with their page numbers. The references at the end of each chapter have been expanded to include each author cited in the text and recast in alphabetical order rather than by subject.

Many other changes in the text have become necessary because of the rapid advances in the medical sciences. New concepts of the nature of disease and its treatment with drugs acting at an enzyme level have been included. Most of the chapters have been expanded, owing to the availability of many new drugs.

Generally used drugs are discussed in detail, those that are no longer in current use are mentioned only: reference is made to previous additions. The 6th edition has been brought abreast of the official compendia. Over 100 new drugs not mentioned in the 5th edition are included in the 6th edition. No effort has been made to include all dosage forms and drug mixtures. For this information the reader is referred to the numerous drug encyclopedias. Drugs in general use, representing types of therapeutic agents; are discussed in detail to illustrate pharmacologic principles. Less frequently used drugs evoking a similar pharmacologic response are not considered as thoroughly.

Generic names are used for drugs which are official in the Pharmacopeia or National Formulary. For nonofficial drugs we have attempted to use the name by which the drug is most commonly known to the medical profession, but the generic name is also included.

The authors are grateful for the many friendly, critical, and constructive suggestions which have come to them from teachers of pharmacology in schools of medicine, dentistry, pharmacy, and veterinary medicine. We welcome further comments.

In the revision of the text, which involves many areas of clinical medicine, we employed the same policy used in preparing the original manuscript, *i.e.*, sending sections of the text to various specialists for criticism and review. This help has been of inestimable value. To the following specialists who have served in this capacity we are greatly indebted:

Food and Drugs Act
Hon. George P. Larrick
Commissioner of Food and Drugs

Response of Cells to Drugs
John J. O'Neill, Ph.D.
University of Maryland

The Sulfonamide Drugs
William P. Boger, M.D.
Montgomery Hospital, Norristown, Pa.

Tuberculosis Chemotherapy
Lt. Col. Warren C. Morse, MSC
U. S. Army Medical Research and Nutrition Laboratory

Skin and Mucous Membranes
Harry M. Robinson, Jr., M.D.
University of Maryland

Ear, Eye, Nose, and Throat
Samuel L. Fox, M.D.
University of Maryland

Introduction to Central Nervous System
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University of Maryland

Alcohol and Alcohols
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University of Maryland

Anesthesia
Frieda G. Rudo, Ph.D.
University of Maryland

Drug Addiction
Hon. Henry L. Giordano
Commissioner of Narcotics

Sympathomimetic Amines
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University of Stockholm

Nicotine and Tobacco
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Medical College of Virginia

Response of Myocardium to Digitalis
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New York University

Response of Myocardium to Antifibrillatory Drugs
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University of Maryland

Response of Coronary Vessels to Drugs
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University of Maryland

Anticoagulants
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Marquette University

Hematopoietic System
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University of Maryland

Response of Uterus to Drugs
Ervin E. Nichols, M.D.
Loma Linda University

Sex Hormones
Arthur L. Haskins, M.D.
University of Maryland

Dysmenorrhea
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Richmond Memorial Hospital

Metabolic Effects of the Adrenal Corticotropic Hormone and Adrenocortical Steroids and the Treatment of the Arthritides
Adalbert F. Schubart, M.D.
University of Maryland

Insulin and Diabetes
Mary A. Root, Ph.D.
The Lilly Research Laboratories

Thyroid and Iodine Metabolism
Sidney C. Werner, M.D., Sc.D.
Columbia University

Calcium-Phosphorus Metabolism
J. Edmund Bradley, M.D.
University of Maryland

Cancer Chemotherapy
Arnold M. Seligman, M.D.
Sinai Hospital, Baltimore

In addition to the foregoing reviewers we are indebted to Sylvan Forman, Ph.D., for checking the chemical formulas in the text, to George J. Cosmides, Ph.D., for drawing chemical formulas, and to Robert S. Rozman, Ph.D., for preparing the index. We are grateful to Miss Eleanor D. Rose and Mrs. Evelyn Volkman for the collating, organizing, and typing of the material for this revision.

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*Arlington, Virginia*

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# PART I

## THE HISTORY OF PHARMACOLOGY, PHARMACOLOGIC PRINCIPLES, AND AN INTRODUCTION TO DRUGS

## 1

## *The Scope of Pharmacology*

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*Pharmacology* is the science that deals with drugs. *A drug is a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animals.* The word drug is derived from the French word *drogue*—a dry herb. Pharmacology in its broadest sense embraces all of the knowledge concerning drugs. The word pharmacology is derived from the Greek words *pharmakon* (drug) and *logos* (a discourse or treatise), and hence includes such allied fields as *pharmacy*, *pharmacognosy*, *toxicology*, *posology*, *chemotherapy*, *therapeutics*, and *materia medica.* Each of these subdivisions of pharmacology is a highly specialized field and makes its contribution to our composite knowledge of drugs.

The Federal Food, Drug and Cosmetic Act defines a drug as follows: The term *drug* means (1) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals.

In the health professions the application of pharmacologic knowledge to the diagnosis of disease is illustrated by the use of radiopaque substances and the excretion of dyes; its application to the prevention of disease, by the use of antiseptic drugs; its application to the cure of disease, by the use of the sulfonamides and the antibiotics in infectious diseases; and to the alleviation of symptoms, by the use of morphine in traumatic pain. A knowledge of pharmacologic principles is also essential for the maintenance of optimal health, as illustrated by the use of hormones and vitamins.

### The Subdivisions of Pharmacology

**Pharmacy** is concerned with the collection, preparation, and standardization of drugs. Its scope includes the cultivation of plants which serve as drugs, the synthesis of chemical compounds of medicinal value, and the chemical analysis and testing of the agents used for medicinal purposes. The pharmacist is responsible for the manufacture of *dosage forms* of drugs, such as tablets, capsules, and sterile solutions for injection. He compounds prescriptions for drugs.

**Pharmacognosy** is the science of identification of drugs. The scope of the pharmacognosist is confined to drugs of vegetable and animal origin. He is concerned with the characteristics of various species of plants, their gross and cellular structures, and also characteristics which serve as means of identification. He is also concerned with the biochemistry of plants (biosynthesis), molds, fungi, sera, and vaccines.

**Toxicology** is the science of poisons. It is concerned with the mechanism of action of poisonous substances on living organisms. Further, the symptoms produced by the ingestion of poisons frequently shed light upon the mechanism of the action of the poison if it is administered in smaller doses as a drug. As a medico-legal officer, the toxicologist is concerned with the chemical detection of poisons where criminal intent is suspected. Also, from the point of view of environmental hygiene, the toxicologist is useful in determining the toxicity of industrial dusts and vapors in order to protect the health of individuals exposed to these hazards.

Another important phase of toxicology is the selection of antidotes for poisons. This phase of the science is of great importance to the physician, for he is frequently called upon to treat an individual who has accidentally or purposefully ingested a poison. It has been estimated that the number of chemical agents now available in the home, office, shop, or farm which are capable of eliciting toxic symptoms upon ingestion exceeds 15,000. This number will undoubtedly increase. To meet this emergency there are now in the United States over 200 Poison Control Centers. These are associated with hospitals and medical schools. They are designed to assist the physician in the identification of toxic agents and to familiarize him with the most effective antidotal procedures in cases of intoxication. Through the National Clearinghouse for Poison Control Centers valuable data are being collected relative to the agents most frequently causing poisonings and the best treatment procedures. The practicing physician should have contact with the poison center in his community.

**Posology** is the study of dosage. It is an important division of pharmacology. A knowledge of the dose of commonly used drugs is an essential factor in acquiring confidence in prescribing. Doses vary with individual tolerance and susceptibility. Generally speaking, a dose of a drug may be considered that quantity which is required to elicit the desired therapeutic response in the individual. In brief, it is "*enough.*"

**Chemotherapy** is the use of chemical agents in the treatment of infectious diseases. Substances so employed are referred to as *chemotherapeutic agents.* These agents are designed to kill the invading organisms without harmful effects upon the host.

**Therapeutics** in its broadest sense may be considered as any measure which is taken in the treatment of disease. The word in Greek means the *art of medicine.* The pharmacologist is primarily concerned with one branch of therapeutics, namely, pharmacotherapy, *i.e.*, the administration of drugs to the sick. This is in contradistinction to physiotherapy and psychotherapy, measures which do not involve the use of drugs. Naturally, the physician is fundamentally interested in pharmacotherapy, and it is this phase of pharmacology which makes the greatest contribution to medicine.

**Materia medica** is the division of pharmacology that treats of the sources, description, and preparations of drugs. It is an older term and its use in medicine appears to be diminishing. Years ago materia medica had a prominent place in the medical curriculum as a didactic, descriptive body of knowledge concerning drugs. It has now been replaced by the experimental science of pharmacology.

Pharmacology is the study of *the response of living organisms to chemical stimuli.* One may further divide the subject, from a medical viewpoint, into *pharmacodynamics* and *pharmacotherapy.* The former is concerned with the response of living organisms to chemical stimuli in the absence of disease. The latter branch of pharmacology, pharmacotherapy, deals with the response of the organism in a pathologic state to chemical stimuli. This is the phase of pharmacology which is of special interest to the physician; it includes the treatment of the sick with drugs and therefore is of prime importance in the practice of medicine. It is fundamental to the health economy of any people. Pharmacology affects all levels of physiologic organization, from the cell to society as a whole.

The foregoing definition of the science of pharmacology is a comprehensive one, and it is of interest to view the scope of this science. The action of insecticides on plant and animal cells and the health hazards involved in their use, the response of bacteria and animal parasites such as intestinal worms and amoebae to chemical stimuli, the treatment of diseases of poultry and cattle, and chronic intoxication that might be caused by the ingestion of chemical agents added to food products are all problems of concern to the pharmacologist. Although these and other ramifications of the science have a broad public health implication, the primary concern of the physician in this science lies in pharmacotherapy.

One might well inquire about the interest of the physician in pharmacodynamics, *i.e.*, the response of tissues to chemical stimuli in the absence of disease. Knowledge of the response of nonpathologic tissues to chemical stimuli is necessary in order to understand the mechanism of the action of drugs. A knowledge of pharmacodynamics often is essential as a basis of pharmacotherapy. Because it is frequently impossible to produce in animals pathologic conditions identical with diseases which occur in man, the pharmacologist may be called upon to study the pharmacodynamic activity of a chemical compound and, through his skill and experience, to offer a prognosis as to its possible use as a therapeutic agent in the treatment of disease in man. Indeed, the study of the response of normal tissues to the action of chemical substances has done much to shed light on physiologic mechanisms and to elucidate the action of drugs that have been used empirically in the treatment of disease.

### Pharmacology and the Basic Medical Sciences

Although pharmacology is one of the youngest of the basic medical sciences, its scope is constantly enlarging and its contribution to therapy has made its position in medicine an important one. Its relationship to the other medical sciences is interesting and enables one to understand better the position of this science in the training of a student in medicine.

*Physiology* is concerned with the function of the systems of the living organism. *Biological chemistry* deals with the changes in composition of matter which occur in the processes of life. *Pathology* treats of morphologic, functional or chemical changes and imbalances which may occur to the normal organism. Pharmacology uses chemical stimuli to produce changes in function and sometimes in the morphology of living systems; this is pharmacodynamics. When a living system is in imbalance through distortion of normal bodily processes, a pathologic condition is present; it is then that the chemical stimulus, the pharmacologic agent, the drug, is administered to attempt to reestablish the organism in a normal physiologic and chemical balance. In the parlance of the clinic, a drug is administered to alleviate symptoms and possibly to cure the diseased condition. Examples will serve further to show this relationship between the sciences.

Let us consider the trihydric alcohol glycerin $C_3H_5(OH)_3$. As a product of digestion from edible fats, its fate in the body concerns the biological chemist. He is interested in the fact that it can serve as a precursor of glycogen. The steps of its catabolism in the body from glyceric aldehyde to carbon dioxide and water constitute an important metabolic pattern of the fate of this substance in the animal organism. Substances of this character which serve essentially as foods are not the primary concern of the pharmacologist. If, however, one replaces the 3 hydroxyl groups in the glycerin molecule with 3 nitrate radicals, producing glyceryl trinitrate $C_3H_5(NO_3)_3$, the compound no longer serves as a food. The oily glyceryl trinitrate, in exceedingly small doses, dilates the blood vessels, causing a fall in blood pressure. The coronary arteries share in this dilatation and hence glyceryl trinitrate serves as a drug and has been thoroughly studied by the pharmacologist. It is used in the treatment of coronary artery disease.

The effect of ethyl alcohol $C_2H_5OH$ on the animal organism is intriguing and illustrates the divisions of interest among the basic medical sciences. When ingested in small quantities, alcohol produces no symptoms. It is metabolized, producing carbon dioxide and water, and each gram gives rise to 7 calories. Hence in small quantities alcohol serves merely as a food, and its fate in the body is mainly a biochemical problem. In larger amounts alcohol profoundly affects the central nervous system, causing a depression of the inhibitory centers in the brain and producing the pharmacologic syndrome of inebriety. This phase of the action of alcohol brings it immediately within the scope of pharmacology, and as a drug it has been extensively investigated.

The physiologist studies the effect on the living organism of hydrocortisone as a product of a gland of internal secretion. The action of hydrocortisone on the organism under stress and its effect on metabolism are of prime physiologic importance. The pharmacologist has an interest in this compound as a product from the adrenal glands, available as a therapeutic agent. It is a potent drug, useful in the treatment of arthritis and certain other diseases.

Indeed, one can readily judge from the examples cited that there are no sharp lines of demarcation among the basic medical sciences. The overlapping is frequent and extensive; in fact, the student must view the basic medical sciences as a specialized study of biology. These sciences are the study of the human body in health and in disease, structurally, functionally, and chemically. When outside chemical stimuli are introduced, we designate the study as *pharmacology*. It is clear that these divisions of the sciences are man made. They are useful for the systematizing of knowledge. The ultimate purpose of each is the same, *i.e.*, *understanding of life processes and the utilization of this knowledge for the health of mankind.*

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# 2

# The Historical Development of Pharmacology

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**Introduction.** Fighting disease with drugs is a timeless struggle. Its beginnings echoed out of the primeval jungle. Man's survival on this planet has depended upon its success. Today the conflict continues unabated in laboratory and clinic. The scientific approach to this struggle is pharmacology.

**Paracelsus.** There are several significant events in the history of science which led to the development of pharmacology as a separate and distinct medical discipline. One of the first of these was the life and work of the Swiss physician-chemist Paracelsus. Paracelsus appeared upon the European scene at the beginning of the Renaissance. He was a contemporary of Columbus, Martin Luther, and Michelangelo.

Prior to the time of Paracelsus the purpose of chemistry had been to search for the philosopher's stone, a fictional charm which would confer perpetual youth and convert the baser metals into gold. Paracelsus appeared upon the stage of science and medicine not as a careful experimenter, but as a timely iconoclast. He thundered his stirring message through the ranks of the medical and chemical practitioners of his time. "The purpose of chemistry is not to make gold but to study the fundamental sciences and turn them against disease. Not gold but medicine is the purpose of chemistry," he declared. The message of Paracelsus deeply penetrated the fabric of chemistry and enlisted this dynamic science as a progressive ally of medicine. It portended the synthesis of thousands of compounds for pharmacologic testing and possible therapeutic use.

**Cinchona and malaria.** In 1630 the use of Peruvian bark in the treatment of malarial fever was discovered. It became known as the cinchona bark. From this bark two centuries later the French pharmaceutical chemists Caventou and Pelletier isolated the alkaloid *quinine*, the first *specific drug* to be used in an infectious disease. As medicine progressed, the use of quinine treatment in malaria required pharmacologic study in order to determine a rational basis for the therapy. Besides, other compounds related to quinine demanded study, and the necessity for the skills of the pharmacologist became obvious.

**Arsenic linked to carbon.** In 1760 Louis Cadet, apothecary to the French army, made cacodyl oxide $(CH_3)_2As{-}O{-}As(CH_3)_2$ by heating together potassium acetate and arsenious oxide. This was the first time that man had succeeded in attaching an arsenic atom to a carbon atom. The experiment portended the synthesis of the organic arsenicals. It meant that the toxicity of this potent element, arsenic, could be modified by combining it in a multiplicity of organic molecules. Pharmacologic studies would be necessary, and they followed, but nearly two centuries elapsed before Paul Ehrlich made the organic arsenical arsphenamine and used it successfully in the treatment of syphilis.

**The purple foxglove.** In 1783 the English physician William Withering published his epoch-making monograph on the use of digitalis, entitled, "An Account of the Purple Foxglove and its Medicinal Use." Withering used digitalis in the treatment of dropsy and believed that the drug had a direct action upon the kidney. How the drug acted was a puzzling question. The exploration of its many possibilities in therapy became a problem of pressing medical importance. The answers to questions of this character strongly suggested the necessity for a new science. Later, pharmacology supplied many of the answers to these questions.

**Morphine and other alkaloids.** The German apothecary Sertürner isolated from opium the alkaloid morphine in 1807. He showed by experiments on dogs that most of the narcotic activity of opium was dependent upon morphine. This was the *first alkaloid* that was isolated from a plant. It was a forerunner of the rapid series of discoveries in this field which were to follow. Shortly thereafter, strychnine, caffeine, emetine, atropine, and quinine were separated as pure crystalline alkaloids. Morphine elicited intriguing reactions from living organisms which required pharmacologic study. Later, in the nineteenth century, the first pharmacologist, *François Magendie,* was to study the pharmacologic action of these compounds. But a distinct medical science of pharmacology appeared to be warranted.

**Wöhler and urea.** One of the most significant events in the history of mankind was the synthesis of urea by Wöhler in 1828. It ranks with the great discoveries of the ages. Wöhler made urea from ammonium cyanate $NH_4OCN \rightarrow (NH_2)_2CO$ by the evaporation of an aqueous solution of the latter. He had made urea without a kidney. But what is more, he had synthesized an *organic* chemical compound without the intervention of the mysterious *vital force.* He had begun an era in chemistry and had laid the basis for the changing of the character of civilization. Organic chemistry, carbon chemistry, was to develop from this experiment. The chemist was to become a creator. More than a million new chemical entities would appear, and are now produced at the prodigious rate of about 30,000 per year. New dyes, new plastics, and new perfumes were made. But what about new drugs? A science was needed that had for one of its purposes the constant screening of these new creations of matter in order to determine their possible usefulness as therapeutic agents. This science was destined to be pharmacology.

**Christopher Wren and the hypodermic needle.** In the middle of the seventeenth century at Oxford University Christopher Wren and Robert Boyle showed that a quill inserted into the vein of a dog provided a means of injecting drugs directly into the blood stream. Based upon these studies, the hollow hypodermic needle was developed in 1853 by Alexander Wood of Edinburgh. The invention was destined to exert a tremendous influence on drug administration. No longer was it necessary to administer drugs orally, rectally, or by inhalation. The hypodermic needle made it possible to inject drugs directly into the blood stream, and dependability and rapidity of action were thus achieved. Needless to say, the hollow hypodermic needle has been a device of revolutionary importance in the field of therapeutics.

Thus by the end of the nineteenth century the need for the science of pharmacology was well recognized in Europe and England, where some studies in experimental pharmacodynamics were being carried out in the foremost medical centers. Most of the work, however, was done in the laboratories of biological chemistry and physiology. Pharmacology as a definite medical discipline had not yet made its formal debut.

**Pharmacology as a medical science.** These discoveries in the field of science pointed to the medical need for pharmacology. Thus, emanating from a background of mystery and magic, from folklore and empiricism, the medical science of pharmacology emerged coincidental with the turn of the century. It was necessary to bridge the gap between the manufacturer and the prescriber of drugs. It was essential to unravel the mysteries of therapeutics. It was desirable to develop and test the ever-increasing lists of new synthetics and natural products which the organic chemist was making available. Within seven decades, this science has pervaded every area of medicine, from early diagnosis to treatment and cure.

Pharmacology in the United States began with the appointment of John J. Abel as Professor of Pharmacology in the University of Michigan Medical School in 1890. Prior to this time this subject, generally referred to as materia medica, was taught, as a rule, by practitioners of medicine who were not specialists in the field. They taught the subject mainly as a didactic, descriptive body of knowledge related to drugs.

FRANÇOIS MAGENDIE
1783–1855
*The first pharmacologist*

"Facts and facts alone are the foundation of science. . . . When one devotes one's self to experimental research it is in order to augment the sum of known facts, or to discover their mutual relations."

In 1892 Professor Abel was called to the chair of pharmacology in The Johns Hopkins Medical School. Here he did his outstanding scientific work in pharmacology. Abel's approach was different. He had thorough training in Europe under the biochemist Schmiedeberg and had worked with many eminent European clinicians. He considered pharmacology an experimental science. Abel's approach to the subject marked an era. Today he is looked upon as the father of pharmacology in America.

In order to understand the background of pharmacology, let us consider some of the contributions to medicine made over seven decades by this science. Abel's laboratory soon became a mecca of pharmacologic study, and many of the advances in this field were carried out in his laboratory or in the laboratories of his pupils.

**The first hormones.** In 1900 Abel and his associates separated *epinephrine* from the medulla of the adrenal glands. He prepared the material as a benzoyl derivative and in 1902 Takamine separated the base epinephrine in burr-like crystals. Its synthesis was accomplished by Stoltz a few years later. Thus to Abel, and to the science of pharmacology which he represented, belongs the credit of having isolated the first hormone.

In 1905, Reid Hunt, working in Abel's laboratory, obtained an extract from the adrenal medulla that evoked marked depressor responses when injected into cats. Later, Hunt showed that what he had separated from the adrenal glands was *acetylcholine*. Thus within a period of 5 years the respective hormones of the sympathetic and parasympathetic divisions of the autonomic nervous system were discovered in Professor Abel's laboratory, a commendable tribute to the new science of pharmacology.

**The standardization of drugs.** One of the outstanding contributions of pharmacology to medical practice is that of drug standardization. Safety, efficacy, and dependability of dosage depend upon standardization. The chemical methods for the assay and standardization of vegetable and animal drugs developed by the German pharmaceutical chemists and by Dohme and Caspari in this country during the decade 1900 to 1910 were not applicable to all drugs.

Such important agents as digitalis, pituitary extracts, and insulin had to be standardized on living animals. In this field, designated as *bioassay*, the pharmacologist has played an important role. He has developed assay methods for digitalis and with these has made a capricious medicinal agent dependable for use in heart failure. Indeed, aside from the practical applications of bioassays, they have played an important part in research, especially in the isolation of active principles from animal tissues and plants. When a principle is found to elicit a definite pharmacologic response, such as the contraction of smooth muscle or the increasing of the blood pressure, these responses may be used to identify qualitatively the presence of the principle. The magnitude of response may also be used to assay the quantity of principle present. Bioassay is a practical, useful tool in research and medicine and, with certain drugs, successful therapy is dependent upon this phase of pharmacology.

**Arsenic, syphilis, and chemotherapy.** In 1910 Paul Ehrlich announced the preparation of *arsphenamine*, his 606th compound studied as an anti-syphilitic drug. The importance of arsphenamine and subsequent drugs in the cure of syphilis cannot be overestimated. From a pharmacologic standpoint it represented a great achievement. Not only was it the triumphant fruition of years of systematic pharmacologic research, but it represented the first bactericidal synthetic drug with a definite specificity for an invading pathogen. Later, Mapharsen, sulfanilamide, penicillin, and streptomycin were to follow. Ehrlich's synthesis and experimental trial of these arsenical treponemicidal agents were referred to by him as *chemotherapy, which is the use of a definite chemical compound to combat the causative agent of an infectious disease.*

**Diagnosis with drugs.** The use of phenolsulfonphthalein as an agent to measure the functional activity of the kidney was developed in the pharmacologic laboratory of The Johns Hopkins Medical School. The compound was made by the chemist Ira Remsen and given to Professor Abel for testing. Abel was seeking a drug useful by injection that would combat intestinal stasis after laparotomies. He observed that the red dye was rapidly and completely excreted by the kidneys. This dye injection became the standard clinical procedure for measuring the functional activity of the kidneys. The test has been used for half a century, but what is more, it may be considered as a forerunner of the *bromsulphalein liver functional test* and the visualization procedures for the x-ray of the gall bladder. *Iodopanoic acid* is one of the compounds used for the latter procedure.

**Vividiffusion.** The work in the laboratory of Professor Abel exemplifies the wide ramifications of pharmacology. With Turner, in 1913, he intercepted the blood flow from the renal artery of a dog by means of a series of tubes consisting of permeable membranes. Blood passing through these tubes was returned to the circulation. The tubes were surrounded with solutions of the various crystalloids of blood. Crystalloidal substances in the circulating blood diffused out into the surrounding fluid; cells and colloids remained in the blood. This experiment, referred to by Abel as vividiffusion and often called the "artificial kidney," enabled investigators, for the first time, to identify amino acids unconjugated in the blood. Today this ingenious device is used clinically with excellent results, to remove toxic substances from the blood.

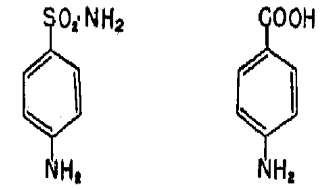
**Posterior pituitary hormones.** In 1919 Abel and his associates obtained from the posterior lobe of the pituitary gland a principle which, when injected, produced a pressor response and also acted upon the uterus, causing its contraction. Abel held the view that the pressor and oxytocic activities of the pituitary principle were due to one molecular entity, and to this view he tenaciously adhered. In 1927 Kamm and his associates showed that the principle separated by Abel consisted of at least two chemical moieties: one, *oxytocin*, was responsible for uterine contraction; the other, *vasopressin*, acted upon the blood pressure. In 1954, du Vigneaud, by a series of brilliant investigations, determined the structure of vasopressin and oxytocin and synthesized these hormones.

**Anti-infective drugs.** Some of the most brilliant successes in pharmacology have been concerned with the bactericidal agents. The development of arsphenamine by Ehrlich has been mentioned previously. Ehrlich pleaded for a drug which would sterilize the blood when infected with streptococci or staphylococci, just as arsphenamine killed the spirochetes. He named such an agent a *magna therapia sterilisans*. In 1920 mercurochrome, which contains a mercury atom attached to a dye molecule, was synthesized. Although active as a local antiseptic, it was too toxic for systemic therapy in septicemias.

In 1927 hexylresorcinol was synthesized and found to have an extraordinarily high germicidal activity. The molecule contains no toxic metal and is comparatively nontoxic to the host. In systemic infections it was found to be of little value because its germicidal activity was not exhibited in the blood. Its synthesis and study were a significant step, however, in the struggle to obtain non-metallo organic compounds of low toxicity, yet of high bactericidal potency.

The next significant advance in this field was in 1935, when Gerhard Domagk's paper showing the use of certain sulfonated dyes in the treatment of streptococcal septicemias appeared in a German clinical journal. The dyes *Prontosil* and *Neoprontosil* were broken down in the body and excreted in the urine partially as *sulfanilamide*. This substance thus made its advent into medicine. Sulfanilamide, a simple, comparatively nontoxic organic molecule, heralded an era in the treatment of infectious disease.

It would be difficult to overestimate the value of these drugs in clinical medicine. However, in the development of other useful anti-infective drugs, the sulfonamides played an equally important role. These drugs pointed the way to the use of drugs with structures similar to those of bacterial metabolites as anti-infective agents. These substances, which resemble in chemical constitution some essential metabolite of the invading organism, are now used extensively in medicine. The structure of the genuine and spurious metabolite is so similar that the organism accepts the substitute in place of its genuine metabolite. Further, the spurious metabolite attenuates or kills the cells which attempt to use it. The phenomenon is illustrated by the competitive action of sulfanilamide and *para*-aminobenzoic acid for certain pathogenic bacteria. Their structural similarity may be seen in the accompanying formulas.



Sulfanilamide *para*-Aminobenzoic Acid

The discovery of this "principle" has stimulated interest in the specific metabolic patterns of different organisms and served as a marked impetus in research in the field of anti-infective drugs.

Following the sulfonamide drugs came the clinical application in 1940 by Chain and Florey of Fleming's discovery of *penicillin* in 1929. Penicillin is active against gram-positive organisms and against certain gram-negative organisms. The drug exhibits an amazingly low toxicity to animals and man. It is this feature of the compound which makes it a landmark in the struggle for better anti-infective drugs. With penicillin man achieved for the first time the long-sought goal, a potent, dependable anti-infective agent with negligible toxicity to the animal host.

Other drugs from molds and bacteria have followed, and the discoveries of *streptomycin* in 1943, *chloramphenicol* in 1948, and the *tetracyclines* in 1952 are outstanding among them.

**New anesthetics.** In 1922 Luckhardt introduced the unsaturated hydrocarbon ethylene into general anesthesia. This was followed by the brilliant suggestion of Leake to combine the essential features of the molecules of ethyl ether and ethylene. This resulted in the synthesis of the hybrid molecule, divinyl oxide, $CH_2{:}CH—O—CH{:}CH_2$. This volatile anesthetic has become a valuable agent, especially for anesthesias of short duration. In 1929 Lucas and Henderson demonstrated the value of the hydrocarbon cyclopropane as a general anesthetic. The usefulness of this anesthetic gas has been demonstrated, and today it stands as one of the principal general anesthetics.

The use of the barbituric acid drugs, such as *amobartital sodium* and *Evipal sodium* as intravenous general anesthetics led to the introduction by Lundy in 1934 of *thiopental sodium* as an anesthetic agent. It is one of the principal anesthetics in use today for induction and anesthesias of short duration.

During the decade 1950 to 1960 rapid advances were made in the field of anesthesia. Numerous new volatile anesthetic ethers and hydrocarbons containing fluorine were synthesized. The presence of a sufficient number of fluorine atoms in the molecule eliminates the explosive hazard of the anesthetic agent. In addition, some of these agents are very potent and require exceedingly low blood levels for anesthesia. The first of these fluorinated agents was *Fluoromar;* it was followed rapidly by *halothane* and *methoxyflurane.*

**Other discoveries.** Chen's introduction of the alkaloid ephedrine into medicine in 1922 heralded the synthesis and subsequent therapeutic use of *amphetamine, phenylephrine, mephentermine, isoproterenol,* and other sympathomimetic amines. These drugs enjoy wide use in the treatment of depressed states, nasal congestion, cardiogenic shock, asthma, and heart block.

The study of analgesic agents and the relief of pain represents a distinct pharmacologic contribution. Small and Eddy have synthesized and investigated hundreds of morphine derivatives. They have shed light on the entire problem of the relief of pain with drugs; even some of the mysteries of addiction are beginning to yield to repetitious inquiries in this field. Other synthetic drugs such as *meperidine* and *methadone* now appear to compare favorably with morphine in the relief of pain. By the synthesis of these drugs man for the first time has achieved his independence from the opium poppy in the relief of severe pain. Furthermore, in 1952, morphine, the principal alkaloid of opium, was synthesized by Gates and Tschudi.

Within the last 25 years three new and interesting types of pharmacologic agents have been introduced into therapy. These are represented by *Dicumarol, Tridione,* and *Benadryl.* Dicumarol is used to prolong the clotting time of blood. Tridione appears to be a specific in the treatment of petit mal epilepsy. Benadryl is a specific antagonist to histamine and therefore has a wide variety of uses in the treatment of various disturbances produced by excessive histamine release. Within these three categories of drugs many variants have been synthesized. Frequently there are therapeutic advantages in having several compounds from which to select the drug of choice. It enables the physician to tailor the drug to the specific needs of the patient.

During World War II many contributions were made to pharmacology. The use of British anti-Lewisite (BAL) as a specific drug in heavy metal poisoning is one of these contributions. The study of many compounds as anti-malarial agents has resulted in the clinical application of *chloroquine* as a superior anti-malarial drug. The release of atomic energy, making radioactive atoms more readily available, has provided compounds containing radioactive atoms for the treatment of polycythemia, hyperthyroidism and other diseases.

During the years immediately following World War II, major developments in pharmacology continued at a rapid pace. Among the substances made available in clinical medicine are *vitamin* $B_{12}$ for the treatment of pernicious anemia, and *cortisone* and other steroids and *ACTH* for the treatment of arthritis and other diseases.

A striking advance in the field of drug therapy was achieved when the value of the alkaloid *reserpine* and the synthetic drug *chlorpromazine* in the treatment of the mentally ill was observed. The change in emotional state and motivational patterns of psychotic patients produced by these drugs is a discovery that has favorably changed the prognosis of a large segment of patients with mental illness. The problem of mental illness no longer appears insurmountable. The many new drugs available for the treatment of psychiatric patients suggest even greater success in this field in the future.

A major breakthrough in drug therapy during the decade 1950 to 1960 was the development of *chlorothiazide* and its congeners as potent diuretics. They have been applied extensively in the treatment of congestive heart failure and hypertension.

We mentioned previously the fact that drugs now affect every level of physiologic organization, from cells to society. A striking and tragic illustration of this assertion was the administration of the hypnotic drug *thalidomide* in 1960 to 1962. This presumably harmless agent, when administered to pregnant women early in the period of gestation, was responsible for the production of *phocomelia* (congenital malformations) in thousands of infants. The profound effect of this chemical agent has had a salutary influence upon the whole problem of drug therapy. It has emphasized the tremendous potentialities for physiologic and morphologic change that a chemical compound may possess when administered as a drug. This knowledge will serve as a warning of the catastrophic consequences that might follow the administration of a chemical compound to a patient. To be more optimistic about this tragic event, one may conjecture that given the precise chemical tool, profound physiologic and morphologic changes in diseased tissues might be achieved, possibly providing a cure for such baffling diseases as cancer and arthritis.

**Summary.** This general review of some of the developments of a pharmacologic nature which have occurred during the twentieth century provides one with a background for the science of pharmacology. It further shows that in its broadest aspects this science affects every area of medicine. It also illustrates the fact that although progress has been stupendous, the future still offers many compelling challenges for research and discovery.

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# 3

# *The Nature and Source of Drugs*

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Pharmacology is concerned with the response of living organisms to drugs. Drugs are obtained from mineral, animal, and vegetable sources, but most drugs are synthetic organic chemical compounds.

**Synthetic drugs.** The most important source of drugs today is the laboratory of the organic chemist. This fact was emphasized in the general consideration of the development of pharmacology. Although we are still dependent upon nature for such important drugs as morphine, digitoxin, and insulin, other equally important substances of medicinal value are products of organic chemical synthesis. Such substances as the sulfonamides, aspirin, procaine, and chloroquine are typical synthetic drugs.

**Mineral drugs.** From time immemorial man has employed mineral substances as drugs. In former years crude natural minerals were often used. Today they are purified and occupy an important place in modern medicine. Elementary substances such as sulfur, iodine, and iron are employed in different dosage forms in the treatment of disease. Free acids such as hydrochloric acid are used as drugs. Metallic hydroxides, like that of aluminum $Al(OH)_3$, are used. Salts are a very important class of mineral drugs: the cathartic magnesium sulfate (Epsom salt), the diuretic ammonium chloride, and the antacid magnesium trisilicate.

When salts are employed as medicinal agents the cation and anion effects of the compound are elicited in the organism. The sodium and chloride ions formed by sodium chloride evoke no pharmacologic response other than the osmotic pressure changes in tissues caused by a greater ion concentration. Frequently in the preparation of medicinal salts, therefore, active anions are combined with sodium, such as in sodium salicylate and sodium iodide. In addition, all of the common sodium salts are soluble. Likewise, pharmacologically active cations are combined with hydrochloric acid and employed in the form of their soluble chlorides, such as mercuric chloride and aluminum chloride. In these two salts the principal actions are those of the mercuric and aluminum ions, respectively.

Comparatively new sources of mineral drugs are the radioactive isotopes. Among these substances, which now have a definite place in therapy, are radioactive iodine ($I^{131}$) in the diagnosis and treatment of hyperthyroidism and radioactive phosphorus ($P^{32}$) in the treatment of polycythemia vera.

**Animal drugs.** For centuries men have employed the organs of animals as drugs in the treatment of disease. Years ago this type of therapy was entirely empirical. Today it stands as one of the great successes in modern medicine. Illustrations of useful therapeutic agents of animal origin are liver in the treatment of pernicious anemia, insulin in the treatment of diabetes, and thyroid powder in the treatment of hypothyroidism. Indeed, it is frequently necessary to process and purify the animal organ source of the drug by means of many intricate chemical and physical procedures in order to obtain an active product in a suitable dosage form. In these steps of purification it is the purpose of the chemist and pharmacologist to separate, if possible, the active therapeutic agent as a chemical entity. This has been accomplished in the isolation of *vitamin $B_{12}$* from liver, *insulin* from the pancreas, and *thyroxin* from the thyroid. Furthermore, thyroxin has been synthesized.

**Vegetable drugs.** The older materia medica was rich in drugs of vegetable origin. Roots, leaves, and barks used by primitive man were the principal means of treating disease with drugs until the beginning of the present century. Although many of the plants used as medicines can no longer be considered within the pale of rational therapeutics, some of them, such as digitalis and belladonna, remain important drugs. What is more, the systematic analysis of the constituents of useful vegetable drugs has shed light on the chemical structures responsible for certain types of pharmacologic activity. Frequently in their efforts the organic chemist and the pharmacologist have not only emulated the naturally-occurring product, but have succeeded in improving upon it. This is especially true in the field of local anesthesia, where the newer synthetic agents are more potent and less toxic than the natural parent plant constituent, *cocaine*.

Plants yield large numbers of constituents which are used in the treatment of disease. Some of these are definite chemical entities and can be classified under the heading of the organic structure into which they fall. Thus *menthol*, from peppermint, is a secondary alcohol and *ephedrine*, from the Chinese plant ma-huang, is an alkaloid, an aryl substituted hydramine.

Often, however, mixtures of substances are employed, the chemical composition of which is not yet understood. It therefore becomes necessary to classify these substances on the basis of their use as medicinal agents. A knowledge of this classification is important when drugs of vegetable origin are used in the treatment of disease. The classification is based largely upon physical properties. The following classes are deemed important to the pharmacologist and practicing physician:

1. Alkaloids
2. Glycosides
3. Oils
   a. Fixed oils
   b. Volatile oils
4. Resins
5. Gums
6. Tannins
7. Antibiotics

**Alkaloids.** One of the most important classes of plant constituents from a medicinal standpoint is the alkaloids. *Alkaloids are basic substances found in plants.* The name signifies that these compounds are alkali-like, because they exhibit basic properties. They are amines and hence may be looked upon as ammonia derivatives. The medicinal alkaloids contain cyclic structures. Some of the pharmacologically potent amines of animal origin, such as epinephrine, are occasionally referred to as *animal alkaloids*.

In general alkaloids are white, crystalline substances. Certain alkaloids which do not contain oxygen in the molecule are liquid. Nicotine, the alkaloid in tobacco, is an important member of this group.

Alkaloids in their free state are as a rule insoluble in water but are soluble in alcohol and the immiscible solvents. Alkaloids combine directly with acids to form well-defined salts, such as quinine hydrochloride and morphine sulfate. These salts are generally soluble in water and alcohol but insoluble in the immiscible solvents.

The alkaloids produce many characteristic color reactions with various reagents. These delicate tests are used to identify alkaloids in tissues by the toxicologist. As a class the alkaloids are precipitated from their solutions by tannic acid, salts of heavy metals, and iodine solutions.

Alkaloids probably occur in plants as waste products of the metabolic process. They represent nitrogenous waste and because of their bitter taste and poisonous nature may serve to protect the plant from being used as food by animals. Alkaloids are present in various organs of the plant, such as quinine in the cinchona bark, atropine in the root and leaves of belladonna, and morphine and other alkaloids in the juice of the opium poppy. The chemical constitution of many alkaloids has been established. Many of them have been synthesized.

Pharmacologically the alkaloids of medicinal plants are very active substances. Generally the medicinal virtue of a plant containing one or more alkaloids resides in these constituents. The structures of these substances show wide variations, as do the pharmacologic actions which they evoke. Thus, morphine, from opium, produces a depressant action on the central nervous system, while caffeine, from tea, evokes a stimulating action in the brain. Atropine, from belladonna, blocks with remarkable specificity the action of acetylcholine on the effector cells of the parasympathetic division of the autonomic nervous system. On the other hand, pilocarpine, from pilocarpus, emulates the action of acetylcholine on these structures and elicits stimulation.

Many of the alkaloids are violent poisons. Strychnine and nicotine in exceptionally small quantities will produce death. In deaths caused by alkaloids, as a class of pharmacologic agents, there is no anatomic lesion in the victim, and thus they differ from deaths caused by salts of heavy metals, caustic alkalies, and strong acids. Deaths caused by alkaloidal intoxication are due to excessive stimulation or depression of one or more of the physiologic systems of the body.

Most of the medicinal alkaloids have been isolated in a pure form from the plants which contain them. Therefore the soluble alkaloidal salts such as atropine sulfate and morphine sulfate have replaced to a great extent belladonna leaf and opium, respectively. Medication with active principles hastens the onset of drug action and increases the dependability of dosage. Then too, the pure alkaloidal salt may be injected, while the crude drug or extracts made from it cannot be injected.

**Glycosides.** *Glycosides are ether-like combinations of sugars with other organic structures found in the vegetable kingdom.* Glycosides are referred to as *glucosides* if the sugar in combination is glucose. Glycosides are reasonably large molecules which may or may not contain nitrogen. If nitrogen is present in the molecule, it does not confer alkalinity upon the compound, as does the amino nitrogen in the alkaloidal molecules. Glycosides do not combine with acids to form salts. When warmed with mineral acids the molecules of glycosides hydrolyze and split off the sugar or sugars in the molecule. The residual structure is called the *aglycone* or *genin.*

The most important of the medicinal glycosides are those found in digitalis. Of these, *digitoxin* is the one which is most generally used. The glycosides from digitalis and other plants, which are called the *digitalis allies,* act upon the heart with a great degree of specificity and are therefore called the *cardiotonic glycosides.*

Another glycoside of less importance is *salicin* from willow bark.

**Oils.** The two classes of oils used as medicinal agents are the *fixed* and the *volatile* oils. The former are mainly the glycerides of oleic, palmitic, and stearic acids. The latter vary greatly in their chemical constitutions.

**Fixed oils.** Fixed oils do not exert any marked pharmacologic action. Many of them, such as olive oil and cottonseed oil, are edible. They are digested and serve essentially as foods of high caloric value. Other fixed oils elicit a specific pharmacologic response when ingested. Thus, castor oil irritates the duodenum, producing peristalsis and evacuation. Cod liver oil and other fish liver oils serve as a rich source of vitamin A.

**Volatile oils.** Volatile oils, as the name indicates, are volatilized by heat. Fixed oils, on the other hand, are not dissipated by heat. Volatile oils are also called *essential oils* and *flavoring oils.* The aromas of plants and flowers reside in the volatile oils contained in the plant. Chemically, volatile oils generally contain the hydrocarbon terpene $C_{10}H_{16}$ or some polymer of it. The terpene fraction of the oil serves as a diluent or solvent for more active compounds present. Thus oil of peppermint contains 50 per cent *menthol,* a secondary alcohol, as its active portion. The remainder is the hydrocarbon diluent. Oil of spearmint contains 50 per cent *carvone,* a ketone, with the remainder of the oil consisting of terpenes. Oil of clove is 82 per cent *eugenol,* a phenol, with 18 per cent terpene.

As a class of pharmacologic agents the volatile oils are active. They are mildly bacteriostatic, hence their use in mouth washes. They act as *carminatives, i.e.,* they cause the relaxation of the cardia and permit the expulsion of gas. In high dilutions the oils act as mild irritants to the gastric mucosa and stimulate the flow of gastric juice.

Certain volatile oils elicit specific pharmacologic responses. Oil of clove is an *anodyne, i.e.,* it relieves pain when applied locally to mucous membranes or abraded skin. Oil of wintergreen, which is almost pure methyl salicylate, is used locally in the relief of arthralgias.

The volatile oils are slightly soluble in water, to which they impart their characteristic odor and taste. Solutions of peppermint and spearmint oils in water (0.1 per cent) are used as solvents and flavors in the compounding of prescriptions. The doses of all volatile oils are small, usually from 0.1 to 0.3 ml.

**Resins.** *Resins are rosin-like substances found in plants, usually formed by the oxidation or polymerization of volatile oils.* Chemically, resins vary, depending upon the plant source from which they are obtained. Many of them are derivatives of *abietic acid.* As a class they are insoluble in water but soluble in alcohol and the immiscible solvents. They dissolve in water in the presence of caustic alkali, forming resin soaps. A familiar example of a typical resin is *pine rosin.* The saps from many trees contain resins.

Many extractive pharmaceutical preparations contain resins and require a high concentration of alcohol to keep them in solution. It is important for the prescriber to remember that when these preparations are diluted with water the resin is promptly precipitated, the result being an unsightly mixture for medication.

**Gums.** *Gums are secretory products of plants.* Chemically they are related to the polysaccharides and on hydrolysis yield molecules of simple sugars. They are dispersible in water, producing thick, mucilaginous colloids. They are precipitated from their aqueous dispersions by alcohol.

Pharmacologically, the gums are comparatively inert substances. They are either digested and utilized as a carbohydrate or are unaltered and unabsorbed from the gastrointestinal tract. In the latter instance, being hydrophilic colloids, they absorb water and add weight to the intestinal contents, which produces evacuation. Typical laxative gums are those obtained from *agar* and *psyllium seed.*

Gums are used in aqueous dispersion as emulsifying agents for oils and suspending agents for insoluble solids. Members of this latter class of gums are *acacia,* called *gum arabic,* and *tragacanth.*

There are other plant products present in medicinal preparations that are of minor importance. Among these are the *gum-resins.* As the name implies, they are mixtures of gums and resins in varying proportions. Myrrh is a drug belonging to this class. *Balsams* are resins or oleoresins (mixtures of volatile oils and resins) containing benzoic or cinnamic acid, or both. *Benzoin* is a drug of this class. *Saponins* are found in many plants. They are characterized by the production of much foam when agitated with water. Generally, they are reasonably large molecules which contain no nitrogen. They inactivate the digestive enzymes of the alimentary tract and rapidly evoke hemolysis. *Digitonin* is a saponin found in digitalis leaves, along with the medicinally important glycoside digitoxin.

**Tannins.** *Tannins are non-nitrogenous plant constituents characterized by their astringent action upon mucous membranes.* They are phenolic derivatives that react with ferric salts to give a blue color. As a class, tannins form precipitates with metallic salts. Tannic acid is a tannin usually obtained from nutgalls, the excrescences of the young twigs of the oak tree. Therapeutically tannins have been used in the treatment of burns and diarrhea.

**Antibiotics.** *Substances produced by or derived from living cells which have a lethal or inhibitory action on microorganisms are termed antibiotics.* These substances are produced by living bacteria, yeasts, molds, and other plants. They are valuable in the treatment of infectious diseases. As a group the antibiotics appear to be chemically unrelated. Penicillin is a complex organic acid. Streptomycin is an exceedingly complex organic base. Chloramphenicol, on the other hand, is a comparatively simple organic molecule containing chlorine. These substances show marked variation in their solubilities and require special dosage forms.

## The Discovery and Evaluation of New Drugs

The physician is constantly confronted with the problem of prescribing new drugs. Pharmaceutical chemists are indefatigable in their efforts to provide an ever-increasing number of medicaments for the treatment of the sick. In the discovery, development, and evaluation of new drugs, programs are planned involving the skills of the following scientific "team": *organic* and *pharmaceutical chemist, biochemist, bacteriologist, pharmacologist, toxicologist, engineer, clinician, statistician, physician,* and *pharmacist.* In the past, one worker may have performed the tasks of several. However, today, with the great increase in the mass of data and technics in each branch of science, specialization is confined to some particular area of research.

The chemist plays an important role in the discovery and development of new drugs. His principal fields of interest include the analysis of known active, naturally-occurring compounds, their synthesis, and the production of new synthetic organic chemicals of therapeutic value.

The point of departure in the search for a new drug is usually a consideration of the structure and pharmacologic response of a natural product. It is assumed that pharmacologic activity is a function of the chemical and physical properties of substances. The chemical structure is then modified in the following manner: (1) shifts are made in the position of functional groups, (2) valence bonds are saturated, (3) acidity or basicity is modified, and (4) variations of configuration about an asymmetric center are made. A slight alteration in structure might enhance the activity of the compound studied. This constitutes a "lead," and subsequent research consists of following these "leads."

Another approach is to screen new compounds of unusual structure for indications of pharmacologic response and action against bacteria, protozoa, and viruses. Today, there are screening centers where new compounds with miscellaneous structures are tested for their value in hypertension, schistosomiasis, cancer, and other diseases. Tests are devised so that the maximal amount of information may be obtained from the available samples.

**Pharmacologic evaluation.** Compounds originating from the foregoing approaches are subjected to rigorous pharmacologic study. The aims of this study are to determine the *toxicity, mechanism of action,* and *possible therapeutic application* of the pharmacodynamic action. The study involves acute and chronic toxicity experiments on several species of laboratory animals. Studies on the metabolism and excretion of the drug must be conducted. The pharmacologic responses elicited by the drug are subjected to qualitative and quantitative study. For example, a drug administered orally produces a depressor response. How is this mediated—through the autonomic nervous system, smooth muscle of the vascular wall, or centrally? The answers to these questions clarify the mechanism of action. The potency and duration of action of the new drug must be compared with that of other known depressor agents. If toxicity and pharmacologic responses are favorable, the drug may be indicated as an agent useful in the treatment of hypertension and made available for clinical trial.

**Clinical testing.** The principal objectives of the clinical trial of a new drug are the determination of the efficacy and safety of the product and the establishment of the optimal conditions of use. Dosage, methods of administration, adjunctive therapy, and precautions that will assure its maximal usefulness must also be determined.

The efficacy of a drug must be considered in the light of the therapeutic value of products already available for the treatment of the condition under study. Furthermore, it is necessary to determine all phases of toxicity and the incidence and severity of untoward reactions. An estimation of the relative safety of the agent is made. The amount of therapeutic benefit that may be obtained and the seriousness of the conditions for which it may be useful are compared with its undesirable properties and toxicity.

The first principle in conducting any clinical trial is that *nothing must be done that may harm the patient.* On the other hand, there is no drug available upon which improvement is not desirable. It is necessary, therefore, for the clinician to have pharmacologic information concerning a new drug before he administers it. He will then be able to forecast the probable effective dose and estimate the duration of treatment. He will select those laboratory tests that should be a part of the clinical studies that will furnish an objective estimate of the efficacy of the drug and information on the early or subclinical manifestations of toxicity.

Another requirement for the suitable clinical trial of a new drug is the presence of a competent investigator who is interested in the problem and has adequate facilities. Moreover, professional and technical assistance must be available to carry out properly the details of the research project. Adequate evaluation of a therapeutic agent requires skillful observation with suitable controls and a critical statistical analysis of the results obtained. It is the clinician who makes the final decision as to the usefulness and safety of a new drug. The clinical evaluation of a new drug often suggests new approaches to therapy. These suggestions should be referred to the pharmacologist and other laboratory scientists; they may initiate a new chain of investigations. From this type of cooperative research an ever-increasing number of dependable therapeutic agents for the treatment of disease reaches the physician.

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# 4

# *The Dosage Forms of Drugs*

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## Introduction

The preceding chapter deals with the sources and nature of substances used as drugs. We shall now consider the dosage forms employed to administer these substances in the treatment of disease. The manufacture of suitable dosage forms comes within the purview of the pharmacist. It is his responsibility to make drugs in the most suitable dosage forms available to the practicing physician. The standardization of the dosage forms is another pharmaceutical service.

The medical and pharmaceutical professions have adopted many standard types of pharmaceutical preparations which serve in most countries as useful dosage forms. The term *dosage form* is rather recent and appears to be replacing the expression *pharmaceutical preparation. A dosage form of a drug is a product designed for administration to the body in the diagnosis or treatment of disease.* It is important for the physician to become acquainted with some of the most important dosage forms of drugs. A knowledge of these is essential for successful prescription writing and achieving the maximal therapeutic response from a drug. Let us consider some of the most important dosage forms.

### VEHICLES

The vehicles or solvents are used for the purpose of dissolving and rendering drugs more palatable. *Waters, syrups,* and *elixirs* are important vehicles.

**Waters** are aqueous solutions of volatile substances, usually volatile oils. They are excellent solvents for saline drugs such as bromides and salicylates. They are frequently used as vehicles in prescriptions intended for digestive disorders. Typical waters are *peppermint, spearmint, cinnamon,* and *anise.*

**Syrups** are solutions of flavoring or medicinal substances in a nearly saturated solution of sucrose in water. Syrups are *demulcent,* or soothing to the mucous membranes of the throat, and are used as vehicles for drugs employed in the treatment of coughs. Typical members of the class of flavoring syrups are *cherry, wild cherry, tolu,* and *cacao.* Simple syrup, which is a solution of 85 gm. of sucrose dissolved in sufficient water to make 100 ml., is also a frequently prescribed sweetening agent. Because of their viscosity, syrups may be used to suspend insoluble solids.

**Elixirs** are hydroalcoholic solutions of medicinal substances sweetened and flavored. *Aromatic* elixir, *simple* elixir, or *orange* elixir, is the popular solvent of this class. It contains about 22 per cent of alcohol. It is colorless but can be colored red by the pharmacist. Elixirs are excellent solvents for many drugs and mask the disagreeable odors and tastes of many substances dissolved in them. *Phenobarbital elixir* and *terpin hydrate elixir* are examples of medicinal elixirs.

### AQUEOUS SOLUTIONS

The aqueous solutions can be divided conveniently into two categories. The first is the class of dosage form known as a *solution* and is intended for oral use. The second is the class known as an *injection* and is intended for *parenteral* use, *i.e.,* to be injected under the skin or into the muscles or veins.

**Solutions** are aqueous solutions of medicinal substances. They are also referred to as *liquors.* Typical solutions are *epinephrine* and *hydrogen peroxide* (*peroxide of hydrogen*).

**Injections** are a class of sterile liquids or suspensions which are packaged in containers which will maintain the sterility, and are intended for parenteral administration.

> In the Pharmacopeia, "the sterile preparations for parenteral use are grouped in five distinct classes, defined as follows: (1) Solutions of medicaments suitable for injection, referred to by titles of the form, *Injection;* (2) dry solids which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for Injections, and which are distinguished by titles of the form, *for Injection;* (3) Solids which are suspended in a suitable fluid medium and which are not to be injected intravenously or into the spinal canal, distinguished by titles of the form, *Sterile Suspension;* (4) dry solids which, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Sterile suspensions, and which are distinguished by titles of the form, *Sterile for Suspension;* and (5) Emulsions of fluids in fluid media, suitable for parenteral administration, which are not to be injected into the spinal canal, and which are distinguished by titles of the form, *Sterile Emulsion.*"

Certain nontoxic bacteriostatic agents may be added to lend permanence to the injection. Injections are available in single sealed glass ampules or multiple dose ampules provided with a closure through which the hypodermic needle may be inserted to remove the contents of the ampule. The Pharmacopeia has established specific requirements for sterility and absence of pyrogens for all injections.

Injections of *insulin, digitoxin,* and *epinephrine* are typical of this class.

### AQUEOUS SUSPENSIONS

The aqueous suspensions are classified as *emulsions* and *mixtures.* The former are suspensions of insoluble liquid substances; the latter are dispersions of insoluble solid substances. In each class, as a rule, a protective colloid is added to increase stability.

**Emulsions** frequently contain fixed oils suspended in water with an emulsifying agent added. The oil is dispersed through the aqueous solution of the emulsifying agent. The oil particles are small and because they are coated, they are not disagreeable to the taste. Emulsified oils are more easily digested than undispersed oils.

Examples of this class of dosage forms are *cod liver oil emulsion* and *mineral oil emulsion.*

**Mixtures.** From a pharmaceutical standpoint, any solid material suspended in a liquid is designated as a *mixture.* Occasionally physicians' prescriptions fall into this category. *Chalk mixture* is a member of this class. *Milk of magnesia* and *aluminum hydroxide gel* may be considered mixtures, in the broadest sense. Dense mixtures of precipitates and supernatant fluid such as these preparations are more specifically termed *magmas.* Each of these magmas is extensively employed.

### ALCOHOLIC SOLUTIONS

**Spirits or essences** are alcoholic solutions of volatile medicaments, usually volatile oils. Spirits are often prepared simply by diluting 10 volumes of oil with 90 volumes of alcohol. In some instances inert coloring matter is added. Some are very popular household remedies, such as *peppermint spirit, lemon spirit,* and *aromatic ammonia spirit.*

These preparations are high in alcoholic content and must be diluted with water before they are ingested. The addition of water causes the precipitation of the volatile oil, which as a rule remains suspended sufficiently for dosage purposes. Some physicians prefer to direct the patient to add the dose of the spirit to a teaspoonful of sugar, through which it is readily dispersed, and then to ingest the sugar.

### Extractive Preparations

Extractive preparations are made from vegetable drugs. They represent a definite quantity of the drug from which they are prepared but do not contain the drug as such. Solutions and spirits contain a definite percentage strength of the drug from which they are prepared; extractive preparations, as the name suggests, contain the extracted medicinal virtues from leaves, roots, barks, or other portions of the plant. The solvent, which is called the *menstruum*, is alcohol or a mixture of alcohol and water. The alcoholic content usually is higher than 50 per cent.

Extractive preparations are prepared by two general processes, *percolation* and *maceration*. In percolation the solvent trickles through a column of the coarsely divided drug until the medicinal virtues are extracted. The drug residue is called the *marc*. In maceration the coarsely divided drug is agitated repeatedly with the appropriate solvent until extraction is considered complete. The drug fiber, cellulose and extraneous matter which does not dissolve in the solvent, is removed by filtration.

There are three dosage forms in this class of extractive preparations. They are *tinctures*, *fluidextracts*, and *extracts*.

**Tinctures** are alcoholic or hydroalcoholic extractive preparations of vegetable drugs. When made from potent drugs they represent 10 per cent of the drug from which they are prepared. When the drug is nonpotent, the tincture is prepared at twice the strength, or 20 per cent. The strength of tinctures of drugs containing alkaloids is based upon the alkaloidal content of the drug from which they are prepared. Certain examples will illustrate this statement.

Belladonna Leaf
  0.35 per cent alkaloids
Belladonna Tincture
  10 per cent belladonna ⇨ 0.03 per cent alkaloids
Opium
  10 per cent morphine
Opium Tincture
  10 per cent opium ⇨ 1 per cent morphine

*Camphorated opium tincture* and *compound benzoin tincture* are other frequently used members of the class.

**Fluidextracts** are alcoholic or hydroalcoholic extractive preparations of vegetable drugs, prepared of such strength that 1 ml. of the fluidextract represents 1 gm. of the air-dried drug. These preparations are more important to the pharmacist than to the physician.

The one member of this class which is very generally used is *aromatic cascara sagrada fluidextract*.

**Extracts** may be obtained by evaporating the solvent from tinctures or fluidextracts. They are plastic in character or may be completely dried and powdered. The plastic extract is called a *pilular extract* and is suitable for incorporating into ointments. The pulverulent extract is called a *powdered extract* and is available for use in tablets and capsules.

The extracts are 2 to 4 times stronger than the drug from which they are prepared. *Belladonna extract* and *cascara sagrada extract* are typical members of this class.

### Solid Dosage Forms

**Powders.** Many medicinal substances are insoluble in the widely used pharmaceutical solvents water, alcohol, and glycerin. Often materials of this kind are administered in their pulverulent form. These are called *powders*. Powders may be mixed with sodium bicarbonate and tartaric and citric acids. When mixed with water, the mixed powder effervesces and charges the water with carbon dioxide, giving the dosage form palatability; such a powder is called an *effervescent powder*. The dose of the effervescent powder may be compressed into a tablet. These effervescent powders are very popular as common household remedies.

**Capsules.** Powders may be packed into hard gelatin capsules. The resulting dosage form is called a *capsule*. These are tasteless, readily swallowed, and rapidly disintegrate in the stomach, where they discharge their contents. Capsules are available in various sizes and are one of the most popular dosage forms.

*Delayed action capsules.* A useful dosage form for drugs has been achieved by coating particles of the active ingredient with an agent that provides intermittent release of the drug in the gastrointestinal tract. Thus a number of tiny particles or beads are incorporated in one capsule. After ingestion some of the particles disintegrate immediately, others after 2 to 4 hours, and still others after 6 to 8 hours. This dosage form provides a uniform medication over a period of 10 to 12 hours. These dosage forms are designated by different manufacturers as *spansules*, *repetabs*, *lontabs*, etc. Other varieties of long-release dosage forms have been introduced in recent years. One of these is called *Gradumet*. Its basic structure is that of a physiologically inert plastic matrix impregnated with the drug. This dosage form provides a controlled release of the medication—an outer covering of the tablet permits a rapid therapeutic effect. Following the initial release, the drug continues to leach out from the plastic matrix. As the process is purely physical, it does not depend upon digestion, the pH, or the motility of the gastrointestinal tract.

**Tablets.** Powders may be subjected to mechanical pressure and compressed into small discoid shapes known as *tablets*. Most compressed tablets contain a tablet filler composed of some inert binding material. Dried starch is frequently added, for when dried starch comes in contact with water it swells, causing the tablet to disintegrate immediately. The average 300-mg. tablet contains 60 to 90 mg. of filler and therefore weighs from 360 to 390 mg. Tablets may be coated with chocolate, gelatin, sugar, or other coatings suitable for improving their taste.

*Tablet triturates.* Powders can be mixed with sugar, milk sugar, or some other inert diluent. They can be made more or less plastic by mixing with 80 per cent alcohol. The resulting plastic mass may be molded into discoid forms and then allowed to dry. These are called *molded tablets* or *tablet triturates*. They are convenient for administering very small dosages. Most tablet triturates weigh about 60 mg. Thus a morphine sulfate tablet triturate of 15 mg. is only ¼ morphine sulfate and ¾ inert diluent. A tablet triturate of 1 mg. of atropine sulfate contains in addition approximately 59 mg. of inert diluent.

When tablet triturates are made under sterile conditions they are available for the preparation of injections. These are called *hypodermic tablets*. Hypodermic tablets are completely and rapidly soluble in water and are convenient for the preparation of injections at the bedside.

**Pills.** When powdered drugs are mixed with adhesive substances like glucose or honey, they may be kneaded into a firm and adhesive mass. This mass may be cut into desirable weights and molded into spherical or ovoid forms called *pills*. Pills become hard upon drying and when old may not dissolve in the alimentary tract. This is one of their disadvantages, and in recent years the pill has been gradually replaced by the tablet and capsule. Pills may be coated similarly to tablets. If the coating is made of keratin, shellac, salol, or cellulose acid phthalate, substances which do not dissolve in the acid juices of the stomach but do dissolve in the alkaline juices of the intestine, the pill is called an *enteric coated pill*. Such coatings serve to protect acid-sensitive drugs from the action of gastric juice.

### Skin and Mucous Membrane Dosage Forms

The dosage forms intended for application to the skin or mucous membranes may be divided into *liniments*, *lotions*, *ointments*, and *suppositories*.

**Liniments** are liquid preparations, applied to the skin by inunction or rubbing. They consist of one or more active ingredients and a liniment base or vehicle. The base is generally a bland fixed oil or alcohol. The massage of the skin is an important feature of liniment therapy. The psychological effect of applying the medicament is another factor of importance. *Camphor liniment*, called *camphorated oil*, and *camphor and soap liniment*, known formerly as soap liniment, are popular.

**Lotions** are liquid preparations, applied to the skin without inunction. Their base is usually aqueous. Glycerin and suspending agents are frequently employed. After application the fluid is permitted to evaporate from the skin, leaving a film of the dissolved or suspended ingredients. The well-known *calamine lotion* is typical of this class.

**Ointments** are semi-solid, grease-like substances intended for local application to the skin. They may be applied to the mucous membranes also.

There are ointment bases which are miscible with water. One of these is *hydrophilic* ointment of the Pharmacopeia, which, among other ingredients, contains *polyoxyl 40 stearate*, a surface-active agent. Polyoxyethylene derivatives such as "Tweens" and "Carbowaxes" serve as completely water-soluble ointment bases.

The usual type of ointment, however, has a petrolatum base which consists of petrolatum and white wax. Most ointments are applied as local agents to serve as *astringents*, *antiseptics*, and *protectives*.

Typical ointments are *sulfur*, *yellow oxide of mercury*, and *zinc oxide*.

**Suppositories** are solid preparations for administration to body cavities. There are rectal, vaginal, and urethral suppositories. Many types of suppository bases are employed. The most common are oil of theobroma (cacao butter) and glycerinated gelatin. The former is a fixed oil which is solid at room temperature but which melts at body temperature. It is well suited for rectal suppositories. These usually weigh 2 gm. and are conical or bullet shaped. The latter is preferable, as the contracting of the anal sphincter will force it into the rectum after it has been inserted beyond its greatest diameter. Rectal suppositories may be used to elicit systemic effects of their active ingredients. The rectal dose is usually double the oral dose.

Vaginal suppositories contain glycerinated gelatin as a base and are usually conical or spherical in shape. They weigh from 4 to 10 gm. They are principally employed to confer antisepsis and as spermatocides.

Urethral suppositories are made with a glycerinated gelatin base. They are pencil shaped and weigh from 2 to 4 gm. They are employed mainly for local treatment.

Having described the most popular dosage forms, we shall now consider the standards and legal requirements for the prescribing and compounding of drugs in this country.

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# 5

# *The Pharmacopeia and Other Drug Compendia*

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Drugs are not to be classified among the ordinary items of commerce. If this were done, the regulations of commerce and competition would be sufficient to control their sale. But drugs affect the health of a people. Therefore it is necessary to have special laws to control their sale and to establish standards of quality and purity. Upon these regulations the uniformity and reliability of dosage depend.

Within each state the standards of drugs are enforced by state health departments. Generally the state bureau or department of food and drugs supervises drug standards. At the Federal level, drug control is enforced by the Food and Drug Administration of the Department of Health, Education, and Welfare. This agency is charged with the enforcement of the Food, Drug, and Cosmetic Act of 1938. Among the standards which the agency enforces, however, are those established by the members of the professions of medicine, pharmacy, and dentistry embodied in the three official compendia mentioned in the Act, the United States Pharmacopeia, the National Formulary, and the Homeopathic Pharmacopeia of the United States.

The salient features of the Food, Drug, and Cosmetic Act of 1938, as amended, which are of special interest to members of the medical profession have been set forth by officers of the Food and Drug Administration. Included are the Kefauver-Harris Amendments of 1962.

Drugs and therapeutic devices must meet the following provisions of the Act and regulations:

1. The article must conform with the strength, purity, or quality which it purports or is represented to possess.

2. The labeling (this includes all printed and graphic matter which accompanies the article) must be truthful.

3. The label must bear the name and address of the manufacturer, packer, or distributor, as well as a statement of the quantity of contents.

4. The label of a drug must bear the statement "Caution: Federal law prohibits dispensing without prescription" if the drug falls in any of the following three categories: (1) any narcotic or hypnotic habit-forming drug or its derivatives specified in the Act or regulations; (2) any drug which, because of its toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary for its use, is not safe for use except under the supervision of a practitioner licensed by law to administer the drug; (3) any drug limited to use under professional supervision by an effective new drug application.

Definition (2) obviously embraces considerations other than toxicity of the drug itself; under the definition, for example, the Administration regards all drugs intended for injection, except insulin preparations, as prescription drugs, because of the method of their use.

Labeling of a prescription drug must include a package insert to accompany the drug to the retail pharmacy, which provides full information as to directions for use, dosage levels, warnings, hazards, contraindications, and other information the doctor needs in order to use the drug safely and effectively. Such full-disclosure information is also required in the labeling of sample packages, etc., sent to doctors and in separate brochures, etc.

Exceptions are made only for prescription drugs for which all such information is commonly known by practitioners.

5. If a drug does not fit into any of the three categories requiring it to be labeled as a prescription drug, its labeling must bear adequate directions for lay use. Such directions include indications for administration and adequate directions to permit the drug to be used safely by the layman.

6. The labeling must bear adequate warnings against use by children or in those pathologic conditions where its use may be dangerous to health; and such instructions against unsafe dosage, methods, duration of administration, or application as are necessary for the protection of the user.

7. The article must not be dangerous to health when used in the dosage or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

8. Drugs intended for use by man must bear labels warning against habit formation if they contain any of a list of narcotic or hypnotic habit-forming substances or any derivative of such substances which possesses the same properties. These labels must bear the statement "Warning—May be habit forming" beside the declaration of the quantity of the drug.

9. Drugs which are described in the United States Pharmacopeia, the National Formulary, or the Homeopathic Pharmacopeia of the United States must conform to the specifications of those compendia, including the packaging and labeling requirements, except that deviations in strength, quality, and purity are permitted if the labels bear statements of the nature and extent of such deviations.

The label of every drug must bear the "established name" of the drug and of each active ingredient in the product, and, whether active or not, the quantity, kind and proportion of certain specified ingredients including alcohol, bromides and other drugs whose presence must be known for safe administration.

The labels of prescription drugs must bear, in addition to the above, the quantity of each active ingredient. On prescription drug labels, the "established name" must appear in direct association with the corresponding proprietary name and in type at least half as large as that used for the proprietary name.

10. A new drug may not be distributed until an application establishing its safety for use, after adequate testing, has been submitted and becomes effective. A "new drug" is any drug which is not recognized among experts qualified by scientific training and experience to evaluate drugs as safe for use under the conditions prescribed or recommended in the labeling. During the period that new drugs are under investigation by experts, the label of the drug must bear the statement "Caution: New drug—limited by Federal law to investigational use."

11. A drug which consists wholly or in part of insulin, penicillin, streptomycin, chloramphenicol, chlortetracycline, or bacitracin, their derivatives, or any other antibiotic intended for human use must be from batches which have been certified by the Food and Drug Administration.

12. The following provisions of the Act relating to prescriptions are of special concern to physicians and pharmacists: (1) a prescription is an order to the pharmacist for a single filling unless otherwise designated by the physician; (2) prescriptions for usual drugs may be telephoned to the pharmacist; (3) authority for the refilling of a prescription may also be given by telephone; and (4) the pharmacist must maintain a record of telephoned prescriptions and prescription refills.

There are several regulations in the amended Act that are of special importance to physicians. They are set forth as follows.

1. New drugs must now be proved effective as well as safe before marketing.

2. Experimental drugs: animal tests reasonably establishing safety must be submitted to FDA before human clinical trial. Animal test data, together with any other information regarding safety or efficacy of the drug, must be made available to the clinical investigators. Clinical trials may be conducted only by persons qualified by training and experience. Patients must be informed that an experimental drug is being used, and their consent must be obtained unless it is not feasible, or unless in the professional judgment of the investigator it would not be in the patient's best interest. The investigator must maintain complete records of the use or other disposition of the drug, and case histories of his patients.

3. Cancellation of new drug approvals: new drug approvals may be canceled immediately if the Secretary finds there is imminent danger to health. A previous approval can also be revoked, after opportunity for a hearing, if it appears that safety is not established, or manufacturing methods, facilities or controls are inadequate.

4. Drug names: FDA may establish "official" names for drugs and ingredients when desirable in the interest of usefulness and simplicity. The established name—whether the name in an official compendium, or the officially designated name, or the common or usual name—must be used on labels and in labeling. In addition, all labels, labeling and advertising of prescription drugs must carry the established name of the drug and its active ingredients wherever a brand name of a drug or ingredient appears. The established name must be printed in type at least half as large as the brand name.

5. Advertising of prescription drugs: labeling and advertising of prescription drugs must also give the amount of each active ingredient, and information about side effects, contraindications, and effectiveness of the drug, for the guidance of physicians. This information may be summarized briefly in advertisements.

6. Information to practitioners: the manufacturer must supply the practitioner, upon request, with copies of any and all printed matter required to be distributed with the drug as labeling, or any other printed matter that has been approved by the Secretary.

In addition to these specific requirements for drugs, the following provisions of the Food, Drug, and Cosmetic Act are of particular concern to physicians:

1. Colors for use in coloring foods, drugs, or cosmetics must be from batches certified by the Food and Drug Administration.

2. A food must not be injurious to health. Residues of pesticides used on growing crops and of food additives used in processing, packaging, storage, or transportation of foods must be proved safe by the manufacturer and must be used in accordance with safe tolerances and regulations established by the Food and Drug Administration. The amounts of pesticidal residues that may remain on food crops are also established by regulation. In both cases the regulations are based on scientific evidence of safety submitted by the promoters of such additives or pesticides.

3. Definite labeling requirements and special dietary regulations to cover foods represented for special dietary uses are set forth in the Act.

4. A cosmetic must not contain any substance which may make it harmful to users when used as is customary or as directed on the label.

**The Pharmacopeia.** The need for the standardization of medicinal agents has been recognized for centuries by people in civilized communities. At first the establishment of pharmacopeias or formularies for drugs was a municipal enterprise, such as the Pharmacopeia of London of 1618 and that of Paris in 1639. Later, as means of travel and communication improved, the territorial scope of the pharmacopeias was increased to national proportions. The first national pharmacopeia was the *Codex Medicamentarius* of France of 1819. It was followed by the first United States Pharmacopeia in 1820. This was organized under the strong leadership of Dr. Lyman Spalding. Spalding made provisions for the constant revising of the Pharmacopeia. At first this was done every 10 years. In 1940 the period of revision was reduced to 5 years, with provisions for supplements in order to keep the book abreast of scientific progress. In 1820 the publication of the Pharmacopeia was a private medical effort. In 1850 the pharmacists first took an active part in revision. In 1900 the enterprise was incorporated under the laws of the District of Columbia as the United States Pharmacopoeial Convention.

In 1906, when the first Food and Drugs Act was passed by Congress, the *Pharmacopeia* and its companion book, the *National Formulary*, were given official status under the Act. This status was continued in the new Act of 1938. Thus in this function of drug standardization one observes democracy applied in its fullest meaning. The physicians and pharmacists of the country, through their elected delegates to the United States Pharmacopoeial Convention, establish the standards for drugs in the Pharmacopeia. These standards have the force of Congressional law. And further, the executive branch of the govern-

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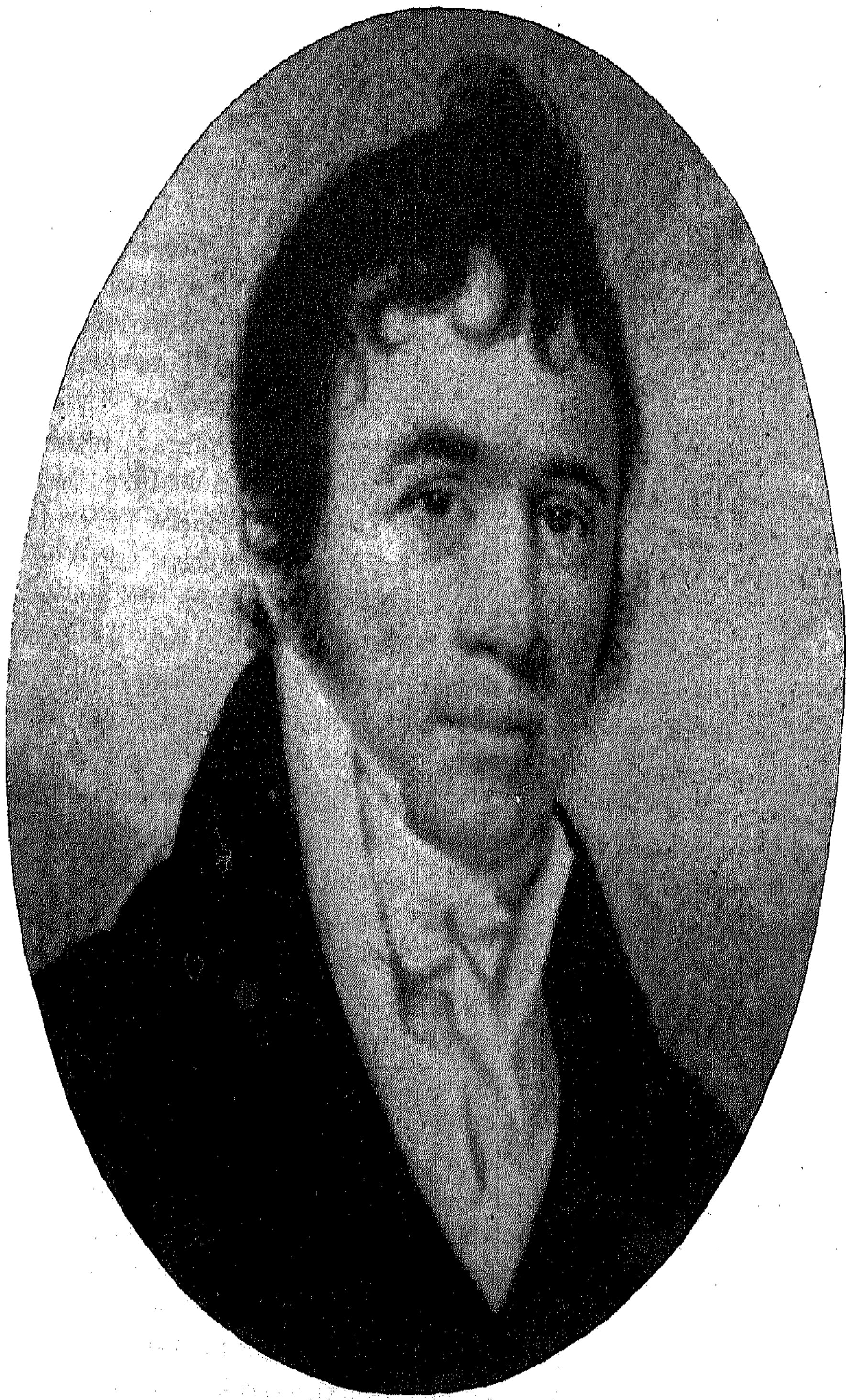

LYMAN SPALDING
1775–1821
*Father of the United States Pharmacopeia*
"The value of a Pharmacopeia depends upon the fidelity with which it conforms to to the best state of medical knowledge of the day."

ment has the police power to enforce these self-imposed standards.

This country is now operating under United States Pharmacopeia XVI, this being the sixteenth revision of the original United States Pharmacopeia. The Pharmacopeia is revised by a group of medical scientists, physicians, and pharmacists who are elected by delegates from colleges of medicine and pharmacy, duly incorporated medical and pharmaceutical societies, and certain government departments. These delegates meet every 10 years in Washington. Revision goes on continuously and is actively supervised by the Director of Revision.

The bases for admission of a drug to the Pharmacopeia are 2-fold. One of these is *therapeutic usefulness* and the other is *pharmaceutic necessity*. The Subcommittee on Scope of the general Committee of Revision, which consists mainly of physicians, determines admissions to the Pharmacopeia, which are based upon proved therapeutic merit. Deletions are also within the purview of

this committee, and drugs which are outmoded or considered no longer efficacious are dropped from the compendium. Flavors, sweetening agents, and suspending agents which are adjuncts to the drugs of therapeutic usefulness are called *pharmaceutic necessities*, and their admission to the Pharmacopeia is determined by the pharmacist members of the Committee of Revision.

The role of the Pharmacopeia is concisely set forth in the preface.

> "It is the objective of a Pharmacopeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage."

Much of the information contained in the Pharmacopeia is of more special interest to the pharmacist and chemist than to the physician. What is important to the physician is that the standards for drugs are contained in the Pharmacopeia and that through constant vigilance these standards are maintained for all official drugs.

The item of special interest to the physician in a pharmacopeial monograph is the dose range. It is an average or usual dose, set forth for guidance to the physician in prescribing. Smaller or larger doses are employed to achieve different therapeutic goals, but the pharmacopeial dose range is the *official dose range* and serves as useful information for the prescriber and the compounder when the question of overdosage arises.

**The National Formulary.** The *National Formulary* is an official compendium for drugs. Its legal status is the same as that of the Pharmacopeia. It is published by the American Pharmaceutical Association. The current eleventh edition became official in 1960. The National Formulary is revised by a committee of the American Pharmaceutical Association, composed of pharmaceutical and medical scientists. Revision goes on continuously.

The principal criterion for admission to the Pharmacopeia is therapeutic usefulness, whereas admissions to the National Formulary are based not only on therapeutic value, but also upon the extent of use. The extent of use of a drug is determined from surveys conducted from time to time by the Committee on National Formulary. On this basis the National Formulary maintains, for limited periods of time, official standards for some of the drugs deleted from the Pharmacopeia. Similarly, National Formulary drugs and dosage forms are frequently admitted to the Pharmacopeia. The National Formulary was originally designed to provide uniform names and formulas for dosage forms manufactured on a small scale by pharmacists for use in filling prescriptions. Many of these dosage forms were complex mixtures which now are recognized as being quite irrational; such forms have been deleted.

The scope and purpose of the National Formulary is: "the establishment and publication of official standards for drugs. The admission of drugs to this edition has been based mainly on therapeutic value as determined by an Advisory Committee on Admissions."

*New and Nonofficial Drugs* (formerly *New and Nonofficial Remedies*) is published under the auspices of the Council on Drugs (formerly the Council on Pharmacy and Chemistry) of the American Medical Association. It has been published annually since 1905. It strives to protect the medical profession and the public against fraud, undesirable secrecy, and objectionable advertising in connection with proprietary medicinal articles. In addition, through comments in the *Journal of the American Medical Association* and *New and Nonofficial Drugs* the Council endeavors to advise the profession "concerning the status of medicinal articles it is importuned to use."

"The function of the Council on Drugs is to examine and evaluate available evidence relating to the actions, uses, dosage, hazards, and other pertinent properties of drugs and to encourage rational therapy by timely, informative reports to the medical profession." Drugs are not evaluated by the Council, if they are well known, *i.e.*, have been recognized in the *Pharmacopeia*, *National Formulary*, or *New and Nonofficial Remedies* (now *New and Nonofficial Drugs*), for a cumulative period of 20 years.

The Council under this new program has expanded its scope. It now appears that the basic function of the Council on Drugs is to evaluate available evidence for the clinical application of all new drugs.

*New and Nonofficial Drugs*, unlike the *Pharmacopeia* or *National Formulary*, contains statements with regard to the pharmacologic action and therapeutic efficacy of its drugs. These statements are prepared with care and represent a fair and concise evaluation of the drug. They are of great importance to the physician.

*Accepted Dental Remedies.* The Council on Dental Therapeutics of the American Dental Association has evaluated dental products since 1930. Those products which have been accepted by the Council are described in their publication, *Accepted Dental Remedies.* A new edition is published each year.

**Other drug compendia.** There are many other compendia containing lists of medicinal agents. The *United States Dispensatory* is a useful encyclopedic type of commentary on official and nonofficial drugs. One of the most useful compilations of currently used drugs is the *Modern Drug Encyclopedia and Therapeutic Index* (*Goodhart*). It includes therapeutic uses. A very useful ready reference book on available drugs and their dosage forms is the *Physicians' Desk Reference*, published annually by Medical Economics, Inc. Furthermore, many of the large hospitals in America have their own special formularies and handbooks. These contain the drugs and dosage forms most frequently prescribed in the institution. They are generally made pocket size, suitable to take directly to the wards.

**United States Adopted Names (USAN).** The term, United States Adopted Names (abbreviated: USAN), designates nonproprietary names of compounds of demonstrated or potential therapeutic interest. Such names are selected by a Council sponsored by the American Medical Association, the United States Pharmacopeial Convention, Inc., and the American Pharmaceutical Association. New drugs are named according to the accepted rules of nomenclature set forth in the appendix of the U.S.P. publication entitled "United States Adopted Names." This provides an orderly and effectual system of name selection for new chemical compounds when they are first proposed for study and evaluation as therapeutic agents. The name selected has no governmental sanction but is intended for use in the United States. The name of a drug does not have legal status until it is admitted to the official standards; the name then becomes "established" or "official."

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# 6

# *The Prescription*

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We have traced the substances used as medicines by man from their origins in nature through their manufacture into suitable dosage forms. In the preceding chapter consideration was given to the laws that control commerce in drugs and the standards which have been established for their identity and purity. Our next consideration is the drug's movement from the pharmacy to the bedside of the patient. From time immemorial this has been done on the order of the physician, and the order is termed a *prescription.*

**History of the prescription.** The prescription is as old as the history of man. In the book of Exodus, the Lord, speaking to Moses directed him to take myrrh, cinnamon, calamus, and other remedies in specific quantities and out of them to prepare "an ointment compound after the art of the apothecary." In the Greek legend, Aesculapius, the god of the healing art, delegated to the beautiful Hygeia the duty of compounding his remedies. She was his apothecary. The physician-priests of Egypt were generally divided into two classes, those who visited the sick and those who remained in the temple and prepared the concoctions of herbs.

In the healing art in ancient Greece there appeared to be a distinct separation between pharmacy and medicine. This condition also prevailed among the Roman practitioners. During the middle ages in Europe there was a marked tendency on the part of the physicians to prepare their own medicines for their patients. The Moorish influence in Europe caused a return to the practice of separate and distinct duties for the physician and pharmacist. The trend of specialization is exemplified by a law enacted by the City Council of Bruges, Belgium, in 1683, forbidding physicians to prepare their own medicines.

Benjamin Franklin was one of the first individuals to separate medicine and pharmacy in America. He appointed an apothecary in the Pennsylvania Hospital whose duties were the preparation of medicines. Dr. John Morgan of Philadelphia was the first teacher of pharmacy in America and advocated prescription writing by physicians. Following the pioneering activities of Morgan, the apothecaries in America established their own societies; the compounding of the physician's prescription is now the principal concern of the pharmaceutical profession. Although in this country many physicians supply medicines directly to their patients, the standard practice is the writing of a prescription to the pharmacist for his compounding. In 1963 it is estimated that physicians wrote 12.8 prescriptions for each family in the United States. From the population survey of family size in the United States, it is further estimated that in 1963 there were between 700 and 800 million prescriptions written. The principal pharmacologic agents prescribed were the internal anti-infective drugs, a category which includes the antibiotics and sulfonamides. The number of prescriptions for the psychotropic drugs is also very large. The cost of drugs constitutes from 19 to 20 per cent of the over-all expenditure for medical care.

**Value of prescription writing.** The custom of having two individuals control the administration of a drug to the sick, as has been pointed out, has withstood the test of centuries. Is it desirable? The pharmacist serves as a constant check on the physician's prescription. He is trained to recognize poisonous doses; he is skilled in detecting incompatibility; and, furthermore, he will assist the physician to medicate with a more efficient and elegant preparation. In addition, a pharmacist who compounds the prescriptions of many physicians will have a huge stock of drugs. The turnover is rapid and the replacement frequent. The physician who writes a prescription has the advantage of a greater selection of drugs and dosage forms, and the possibility of drug deterioration by aging is diminished.

A most dangerous practice, in which, unfortunately, some physicians engage, is that of telling the patient which medicine to purchase at the pharmacy and how to take it. In doing this there is a chance of gross error. For example, a physician directed a young man to purchase some *cream of tartar* at the drugstore and to take a teaspoonful in water. The patient forgot the name of the drug, purchased *potassium chlorate* instead, and proceeded to follow directions. He died three days later of acute nephritis.

It should be emphasized in this connection that before a drug enters the living body there cannot be too many checks to establish its identity and dosage. This is the purpose of the pharmacist. The wise physician will avail himself of his services for the safety and welfare of his patients.

**The prescription form.** A prescription is an order for medicine written by a physician to a pharmacist. To accomplish this the physician could write a note or even a letter explaining each patient's pharmaceutical needs, but this would be time-consuming and cumbersome. Custom has developed a standard abbreviated system of conveying this information.

The prescription is written on a form called a *prescription blank*, as shown.

If a message is worth writing, it deserves to be read. With physicians' prescriptions this is not always possible. Some are written so poorly that even to the skilled pharmacist they are illegible. This is inexcusable carelessness on the part of the physician. Write distinctly.

Tel. ____________
Belmont 041 Reg. No.
John H. Denton, M.D.
211 North Ave. Chestertown, Md.
Office Hours Daily 6 to 8 P.M.
Patient's Name____________ Age ____
Address ____________ Date____
Gm. or ml.
℞
M.D.____
____________

The message on the prescription begins at the symbol ℞. The R stands for the Latin *recipe*, meaning *"take thou of."* The oblique dash across the R is probably a relic of the symbol ♃, that represented a prayer to Jupiter. It is often called Rx, and the symbol for a prescription in medical parlance is ℞. The message of the prescription consists of 2 parts:

1. The ingredients and amounts
2. The directions
   a. To the pharmacist
   b. To the patient

The registry number of the physician is necessary to authenticate a prescription containing a narcotic drug. The name and address of the patient serves as a means of identity between the patient and his medicine. The office hours of the physician are useful to the pharmacist if he wishes to telephone the physician regarding his prescription. The telephone number affords an additional convenience. The age of the patient is important only if the medicine is for a child. It warns the pharmacist to be especially alert for an excessive dose. The date is additional identification. The physician's signature should appear on the prescription. This authenticates the prescription and prevents its falsification. Finally, prescriptions containing narcotic drugs are required by law to be written in ink or indelible pencil. This is an excellent rule to follow for all prescriptions. Dull, blurring pencils may lead to errors.

*English or Latin.* In former years prescriptions were written exclusively in Latin. This accomplishes nothing but possible misunderstanding. The titles in the official compendia are now given first in English and second in Latin. The authors strongly recommend that the physician write his prescriptions in English. It is utterly senseless to introduce the complexity of a dead foreign language into a prescription upon which the life of the patient may depend.

*Abbreviations.* Abbreviations of names of ingredients on prescriptions are permissible. However, as prescriptions today contain fewer ingredients, it is urged that one resort to abbreviations of names of ingredients only when absolutely necessary to save space. Abbreviations have often been the source of misunderstanding.

There are several abbreviations of Latin words used in the directions to the pharmacist and the patient which can be used to advantage on the prescription. They save time, are well understood by the pharmacist, and are considered standard prescription terms.

A list of these useful abbreviations is given below.

| | | |
|---|---|---|
| M. | misce | mix according to the art of the apothecary |
| Ft. | fiat | make |
| Pil. | pilula | pill |
| Cap. | capsula | capsule |
| Chart. | chartula | paper |
| Pulv. | pulvis | powder |
| Aq. | aqua | water |
| āā. | ana | of each |
| q.s. | quantum sufficiat | as much as may be required |
| Sig. | signa | write on the label |
| a.c. | ante cibum | before meals |
| p.c. | post cibum | after meals |
| stat. | statim | immediately |
| q.h. | quaque hora | every hour |
| q.2h., q.3h. | quaque 2 or 3 hora | every 2 or 3 hours |
| o.d. | omni die | daily |
| b.i.d. | bis in die | twice a day |
| t.i.d. | ter in die | 3 times a day |
| q.i.d. | quater in die | 4 times a day |
| p.r.n. | pro re nata | as occasion requires |
| s.o.s. | si opus sit | when required |
| ss | semis | half |
| gtt. | gutta | drop |
| D.t.d. | dentur tales doses | give such doses |
| h.s. | hora somni | hour of sleep or at bedtime |

*Listing of ingredients.* The ingredients of the prescription are listed as a rule in the following order:

1. Active ingredients or basis
2. Agent to modify active ingredient, called *adjuvant*
3. Vehicle or solvent

Customarily, solids are placed before liquids in the prescription listing. Names of all ingredients are capitalized.

**Weights and measures.** In continental Europe liquids and solids are weighed in prescription compounding. In the United States solids are weighed and liquids are measured.

There are two systems of measuring drugs; one is the Metric System, and the other the Apothecaries' System.

The Metric System is the one which is used in continental Europe. It has the following advantages: the units are divided into tenths, the units of volume and length are related, and the units of volume are comparable to the units of weight.

In this country the Apothecaries' System is still used, but it is being superseded by the Metric System. Dosages in this book are expressed in the Metric System.

*The Metric System.* The fundamental unit of measurement of the Metric System is the unit of length. This is the *meter*. It is defined as the distance between 2 lines at 0°C on a platinum-iridium bar known as the *International Prototype Meter* which is deposited at the International Bureau of Weights and Measures. The meter is 1,553,164.13 times the wave length of the red cadmium line in air at 760 mm. pressure and 15°C. It is equal to about 39.37 inches, and is written 1 M.

*Table of capacity.* In measuring fluids, one measures the quantity of fluid contained in a given space. The space which a fluid occupies varies with its character and temperature. One therefore takes the space occupied by water at 4°C. as the standard of comparison.

The unit of capacity is a *liter*, which is the volume of a kilogram of water at 4°C. The liter is divided into deciliters, centiliters and milliliters. The deciliter is a tenth, the centiliter is a hundredth, and the milliliter is a thousandth part of the liter.

Since the liter occupies 1 cubic decimeter of space, the milliliter will occupy one-thousandth part of that, and is therefore equivalent to a cubic centimeter. The term ml., the abbreviation for milliliter, is preferred to cc. (cubic centimeter).

The quantities of medicinal fluids prescribed are usually less than a liter, so in practice the unit ordinarily used in the measurement of fluids is the milliliter (ml.).

*Table of weight.* Solid substances are measured by weight. The unit for measuring weight is the gram, which is the weight of 1 milliliter of water at 4°C.

### *Table of Weights*

1.0 gm. = 1 gram
One-tenth of a gram = 0.1 gm., 1 decigram
One-hundredth of a gram = 0.01 gm., 1 centigram
One-thousandth of a gram = 0.001 gm., 1 milligram (mg.)
One-thousandth of a milligram = 1 microgram (mcg.) or gamma

### *Apothecaries' System*

*Table of weight.* The unit of measurement is 1 grain, which is equal to 0.0648 gm. (64.8 milligrams) in the Metric System. The grain is written thus: gr. i. One gram is equal to 15.432 grains.

### *Table of Weights*

60 grains = 1 dram
480 grains or 8 drams = 1 ounce

*Table of volume.* The smallest unit of measurement is the minim, which is equal to 0.0616 ml. It is written ♏i.

### *Table of Volume*

60 minims = 1 fluid dram (ʒ)
8 fluid drams = 1 fluid ounce (℥)
16 fluid ounces = 1 pint (O)

### *Approximate Apothecary Equivalents of Metric Weights*

Weight

| | | |
|---|---|---|
| One milligram | 0.001 gm. | 1/60 of a grain |
| One centigram | 0.01 gm. | 1/6 of a grain |
| One decigram | 0.1 gm. | 1½ grains |
| One gram | 1.0 gm. | 15 grains (15.432 gr.) |
| One kilogram | 1000.0 gm. | 2.2 pounds |
| 70 kg. man | | 150 pounds |

Capacity

| | | |
|---|---|---|
| One milliliter | 1.0 ml. | 15 minims |
| One liter | 1000.0 ml. | 33.8 ounces or approx. 2 pints |

### *Approximate Metric Equivalents of Apothecaries' Units*

Weight

| | |
|---|---|
| One grain | 0.06 gm. (60 milligrams) |
| One dram | 4 gm. |
| One ounce | 30 gm. |

Capacity

| | |
|---|---|
| One minim | 0.06 ml. |
| One fluid dram | 4 ml. |
| One fluid ounce | 30 ml. |
| One pint | 500 ml. |
| One quart | 1000 ml. |

### *Approximate Household Equivalents*

| | |
|---|---|
| One teaspoonful | 5 ml. |
| One tablespoonful | 15 ml. |
| One teacupful | 120 to 180 ml. |
| One glassful | 240 ml. |

## POLICY IN PRESCRIPTION WRITING

After the diagnosis has been made and the prescription ingredients have been decided upon, the following points should be given consideration in the writing of a prescription.

1. Never give a ready-written prescription.
2. Write deliberately and without hesitation.
3. Avoid rewriting a prescription.
4. Do not converse with the patient while writing.
5. Write legibly—a life is at stake.
6. Warn the patient against the needless prolonged use of the drugs on your prescriptions. State number of refills. This is important because the pharmacist may refill prescriptions only when the physician authorizes him to do so, either in writing or orally.
7. Advise him against recommending the medicine to his acquaintances.

In the choice of ingredients, the following points are to be emphasized.

1. Strive for efficiency and simplicity of medication.
2. Remember that complicated medication multiplies the chance of failure.
3. Choose a single substance designated for a definite therapeutic purpose.

Simple substances should be prescribed unless distinct advantage can be gained by combinations. Indeed, an analysis of prescription ingredients showed that 75 per cent called for a single item.

The patient places great confidence in the prescription which the physician writes. He feels that a special prescription written expressly for his specific condition will do much to help him. The ready-written prescription diminishes this confidence. Hesitation and uncertainty on the part of the physician during the writing of the prescription also shake the patient's confidence.

**Calculation of quantities of ingredients.** It is essential for the physician to acquire a working knowledge of the systems of weights and measures used in prescription writing. Although the metric system is definitely preferred by younger practitioners, there are still many today who prescribe in the apothecaries' system. Therefore a knowledge of the interrelationship between the systems is desirable.

Let us consider the calculation of quantities in several typical prescriptions. Suppose one wishes to prescribe 30 mg. of codeine phosphate as a dose for a cough. The vehicle which is selected is wild cherry syrup. The medicine is to be given every 3 hours. You will see the patient after 3 days. Therefore, assuming he will be taking the medicine for 3 days, he will need about 18 doses. Let us give each dose in the amount of a teaspoonful. This will require 5 ml. × 18 = 90 ml. volume. The dose of codeine is calculated similarly: 18 × 30 mg. = 540 mg. or 0.54 gm. Our prescription is written therefore as follows:

℞
Codeine Phosphate |54
Wild Cherry Syr. q.s. 90|
M.
Sig. Teaspoonful every 3 hours.

Note the vertical line which is the decimal point on the metric prescription. Numerals to the left of it specify whole numbers in ml. or gm.; those to the right of it are fractions. M. is the abbreviation of the Latin "*misce.*" You are directing the pharmacist to prepare a solution. It may be extended to "M. in sol." However, this is obvious and hence unnecessary. Under "Sig." (abbreviation of the Latin "*signatura*") the directions to the patient are given. These will appear on the label. They may have been abbreviated as follows:

ʒi q.3h.

However, the directions completely written out are more desirable.

Let us take another example. Aspirin (acetylsalicylic acid) and phenobarbital are to be prescribed for neuralgia with insomnia. One wishes to give 30 mg. of phenobarbital and 0.3 gm. of aspirin before retiring, for 12 days. The dose of each ingredient is calculated by multiplying the unit dose by the number of doses in the prescription. The prescription is therefore written as follows.

℞
Phenobarbital |36
Acetylsalicylic Acid 3|6
M. in cap. No. 12
Sig. One at bedtime

As a further illustration of the writing of prescriptions for various dosage forms, let us consider a prescription for an ointment. The medication is zinc oxide, an astringent.

℞
Zinc Oxide Ointment 30|
Sig. Use as directed on the skin

Thirty grams are prescribed, a convenient and not excessive quantity of the ointment. The official ointment is 20 per cent, and this strength will be dispensed by the pharmacist. If an ointment of greater or lesser strength is desired, the specific strength must be stated on the prescription.

A prescription which is frequently written in the treatment of grippal conditions is a mixture of caffeine, aspirin, and acetophenetidin. The dose of caffeine is generally 60 mg., with 0.2 gm. each of aspirin and acetophenetidin. Let us write this prescription, indicating the individual dose as follows:

℞
Caffeine |06
Acetylsalicylic Acid |
Acetophenetidin āā |2
D.t.d. Capsules No. 12
Sig. One every 3 hours

Your directions are D.t.d., "*dentur tales doses*" or "give such a dose 12 times." Note āā, which stands for "*ana*" or "of each." This form of prescription writing is infrequent in this country. Its advantage is that only single doses of each ingredient need be prescribed by the physician. The total prescription contents are calculated by the pharmacist.

For the purpose of showing the use of the apothecaries' system of weight and measure in prescription writing, the following typical prescription for gastrointestinal distress is given: phenobarbital sodium, ½ gr.; belladonna tincture, 10♏; compound cardamom tincture, 10♏; and peppermint water. Forty-eight doses are to be prescribed. Drugs of this character are given after meals for long periods of time, and therefore a larger volume is desirable, such as 8 fluid ounces or 240 ml.

℞

| | |
|---|---|
| Phenobarbital Sodium | gr. xxiv |
| Belladonna Tincture | ℥ |
| Compound Cardamom Tincture | ℥ |
| Peppermint Water | q.s. ℥viii |

M.
Sig. ʒi in water p.c.

The calculation of the amount of phenobarbital sodium is as follows: 240/5 = 48 doses × ½ grain = 24 grains. Likewise the calculation for belladonna tincture is carried out as follows: 48 doses times 10 ♏ equals 480 ♏ or 1 fluid ounce, which is expressed ℥. Note the dot above the Roman numeral i. This is to clarify such expressions carelessly written as ℥\\||. Is this 3 or 6? As 3 it is written ℥iii and as 6, ℥vi.

It is important to note that in prescribing liquids it is customary to vary quantities as follows: ⅛,¼,½, 1, 2, 3, 4, 6, 8, 12, 16, or 32 ounces. Bottles made in volumes omitted from this list are seldom found in American commerce.

**Prescription incompatibility.** Incompatible prescriptions result from carelessness or ignorance on the part of the prescriber. If the incompatibility is not corrected by the dispenser, the therapeutic results desired may not be obtained. In some instances the mixture may prove harmful or even fatal to the patient. An incompatible prescription may be defined as one which, after compounding, *vitiates the desired therapeutic effect of its principal ingredients.* Incompatible prescriptions may be divided in a general way into three classes, *therapeutic*, *chemical*, and *pharmaceutical* incompatibility. Incompatibilities often are very serious.

*Therapeutic incompatibility* involves the prescribing together of drugs which have an antagonistic action on the patient. To avoid therapeutic incompatibility, prescribe simple drugs the pharmacologic action of which you understand.

*Chemical incompatibility* embraces the chemical changes which frequently occur in the compounding of prescriptions. They may or may not be of therapeutic significance. To avoid chemical incompatibility, retain a knowledge of the elementary chemical reactions; remember, as a rule, that substances which are used as tests for each other or as antidotes are incompatible. Confer frequently with your pharmacist.

*Pharmaceutical incompatibility* concerns the physical state of the ingredients in prescriptions, usually their solubility. To avoid pharmaceutical incompatibility, prescribe in mixtures, preparations of the U.S.P. and N.F. in which the solvents are similar; confer frequently with your pharmacist.

Observe the following incompatible prescription:

℞

| | |
|---|---|
| Phenobarbital Sodium | 4 |
| Elixir Thiamine Hydrochloride q.s. | 120 |

M.
Sig. ʒi in aq. p.c.

A fine crystalline precipitate of phenobarbital will gradually appear when this prescription is compounded. This reaction is caused by the acidity of the elixir converting phenobarbital sodium into the less soluble phenobarbital. In addition, the neutralization of this acid by phenobarbital sodium decreases the stability of thiamine hydrochloride. It is therefore obvious that a prescription of this kind should be avoided.

**Modern prescription writing.** The modern efficacious prescription is generally a simple one. Complicated mixtures which require much calculation to write and great skill to compound, and which are often of little therapeutic value, are on the decline. Prescriptions for sulfonamide drugs, psychotropic drugs, antibiotic dosage forms, and vitamin preparations are the most frequent.

Many prescriptions today call for a proprietary remedy. Surveys have shown that more than 60 per cent of currently written prescriptions contain at least one proprietary remedy. There is no objection to this if there is no parallel official preparation. Generally the cost to the patient of the proprietary remedy is far greater than that of a similar official preparation which must meet the price of a competitive market. Nevertheless, the prime consideration in making the choice is the welfare of the patient. A prescription for a proprietary remedy has the name of the manufacturer stated on the prescription.

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# 7

# *Methods of Drug Administration and Factors Which Modify Dosage*

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In the preceding chapters we have traced drugs from their origin to the bedside of the patient. In this chapter we are principally concerned with the methods of introducing drugs into the body and the factors which modify their dosage. In addition, we shall consider certain general pharmacologic principles applicable to and descriptive of the administration of all drugs. These principles and their application are of paramount importance to the medical student and to the practicing physician, for the one permanent characteristic of our present medication is change. Frequently a drug whose action the student has learned in the medical curriculum is obsolete before he has had an opportunity to use it in the clinic. It has been replaced by a new agent which is more efficacious and less toxic.

Therefore the student must strive to acquire the principles of pharmacology as they apply to medical practice. He must try to understand the principles which apply, at present at least, to the administration of all drugs. He must learn to think critically regarding the response to drugs and to evaluate his patients' reactions in terms of pharmacologic principles and therapeutic efficacy. In the process of achieving these goals, the student will become a critical observer of his patients' response to drugs. This most admirable characteristic we shall call *pharmacologic perspective.* This perspective should be a critical one. Indeed the word "perspective" is the key, for to know the principles in relation to their application to drugs is more important than to know many specific details. This knowledge is simply the scientific attitude toward drug action. It is a wholesome substitute for pharmacologic credulity.

## Methods of Introducing Drugs into the Body

The chapter on *dosage forms* has given a general idea of the methods of introducing drugs into the body. The principal method of giving drugs is *by mouth*, and doses which are not otherwise specified are assumed to be *oral doses.* The next important avenue of drug administration is the *parenteral method*, which includes all forms of injections. These may be classified as follows:

1. *Subcutaneous*—an injection made by inserting a hypodermic needle through the layers of the skin into the areolar tissue.
2. *Intramuscular*—an injection made by inserting the needle through the layers of the skin deep into skeletal muscle.
3. *Intravenous*—an injection made directly into the vein.
4. *Intrathecal*—an injection made by inserting the needle through the interspinous spaces into the spinal fluid.
5. *Bone marrow*—an injection made by inserting the needle into the marrow of the sternum or other bones.
6. *Intraperitoneal*—an injection into the peritoneal cavity.

All of these forms of parenteral administration have their specific advantages.

*Subcutaneous injections* produce a prompt response, and the dose of the drug is usually about half of that required orally. This form of administration obviates contact of the drug with the digestive juices of the alimentary tract and abolishes the caprice of absorption. Hyaluronidase (see page 941) has been found effective in increasing the rate of absorption of fluids given subcutaneously, including saline, glucose, and Ringer's solution.

*Intramuscular injections* permit the parenteral administration of finely divided insoluble substances in suspension. The onset of action is slow, but the duration of action is prolonged. A depot of the medicament is deposited in the muscle by the injection, and slow absorption occurs. The use of waxes and oils along with the drug is permitted in order to delay absorption and prolong the action. The use of estradiol benzoate in an oil base intramuscularly prolongs the action of this drug. As intramuscular injections often contain suspended particles and may have an oil base, it is imperative that the injection not be made into a small blood vessel. The absence of blood in the tip of the syringe upon pulling the plunger after the needle has been inserted into the muscle will give assurance that the tip of the needle is not in a blood vessel.

*Intravenous injections* elicit a very rapid response. The drug is instantly carried to the tissue upon which it is to act. In general, intravenous injections should be made slowly. Many substances that are very harmful to the surrounding tissues can be injected directly into the blood with impunity. Thus the sodium salts of the sulfonamide drugs with a pH of 10.5 to 11.0 can be injected intravenously without harmful effects. However, it is of great importance to prevent the extravasation of the drug solution into the tissue surrounding the vein.

*Intrathecal* or *intraspinal injections* are used for drugs which do not readily find their way into the spinal fluid. In infectious types of meningitis this kind of injection is especially useful. The production of spinal anesthesia is dependent upon the intrathecal injection of the spinal anesthetic into the subarachnoid space.

*Bone marrow injections* are occasionally utilized when the veins are unavailable on account of their size. The bone marrow injection gives almost immediate response and in this respect is comparable to an intravenous injection. A special type of needle is employed.

*Intraperitoneal injections* are often employed when veins are not available for an intravenous injection. The injection of the drug solution into the peritoneal cavity affords rapid absorption. Comparatively large volumes of solution may be injected.

**Mucosal absorption.** Many drugs are most rapidly absorbed from mucosal cells. The mucosa, therefore, provides an excellent method of administering certain drugs. The tablets of glyceryl trinitrate (nitroglycerin) are administered under the tongue in the treatment of anginal pain. In fact, absorption is so prompt that relief begins within 1 to 5 minutes after the tablet is placed under the tongue. This route of administration bypasses the portal circulation. For this medication, where promptness of effect is so important, the sublingual use of glyceryl trinitrate is more efficacious than its oral administration.

The *rectal absorption* of drugs is also prompt and efficacious. Suppositories may be employed for this purpose. Hypnotic drugs are sometimes given rectally. Theophylline is often used rectally in the treatment of the nocturnal spasm of asthma. As a rule, the rectal dose of most drugs is about double the oral dose. The rectal absorption of many drugs is more capricious than when the drug is administered orally. The method has advantages in the administration of nauseating drugs, in cases in which the oral route is not available, and when prolonged nocturnal action is desired, such as in the treatment of asthma.

The *nasal septum* quite readily absorbs certain drugs placed upon it. It has been used as a successful method of administering posterior pituitary powder in the treatment of diabetes insipidus. The advantages of this method appear to be few, and it is seldom used as a method of drug administration.

*Inhalation.* Volatile compounds may readily be administered by inhalation. Gaseous and volatile liquid anesthetics are administered in this manner. The Benzedrex inhaler represents a less dramatic form of medication by inhalation. Penicillin aerosols in oxygen have been found very effective in treating respiratory infections with this drug. Inhalation therapy is prompt; contact with the blood through the alveolar membrane is abundant. With very volatile substances, inhalation approaches intravenous therapy in rapidity of action.

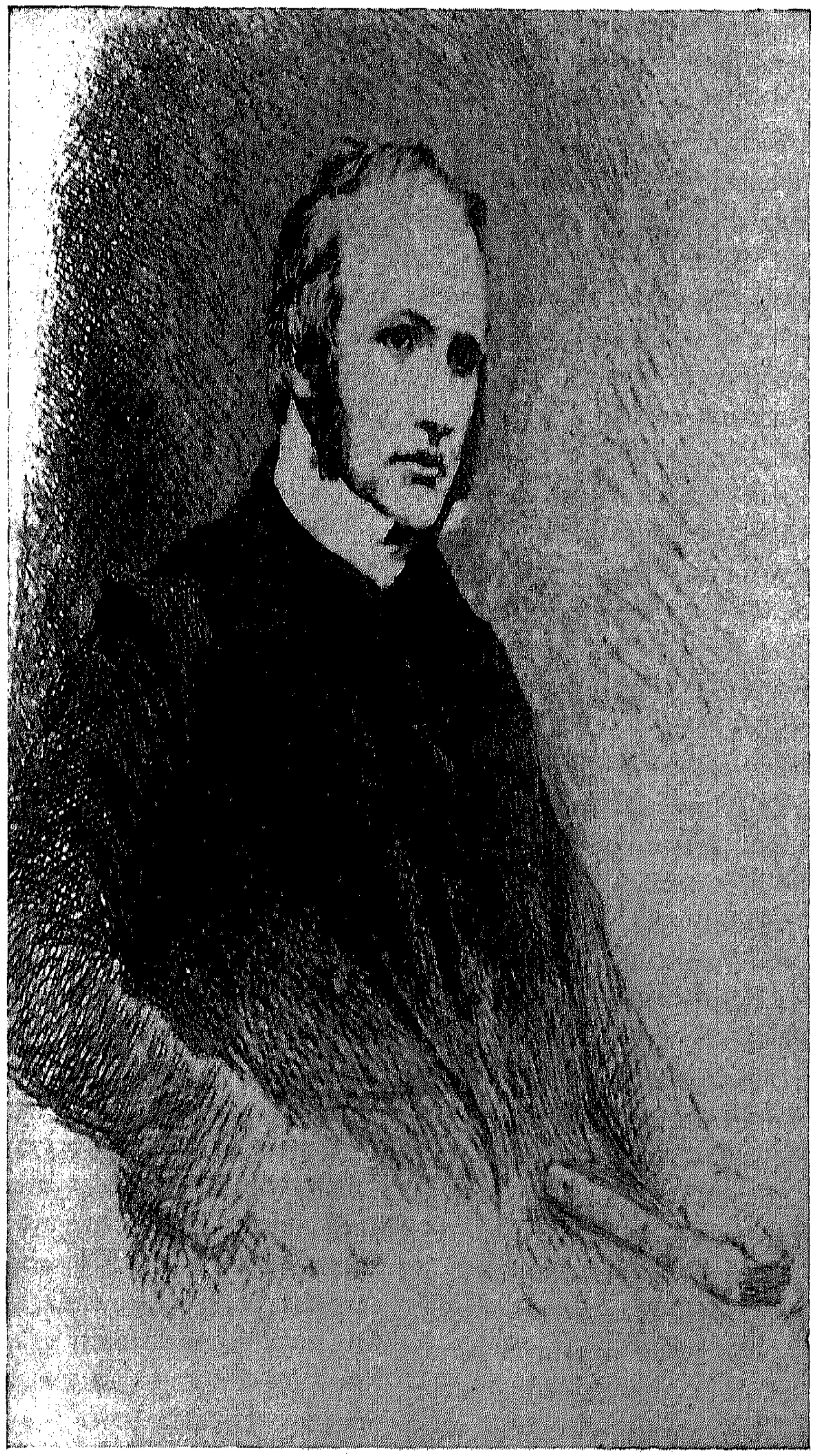
**Jet injection.** In 1947 the first change in injection technic since Alexander Wood's introduction of the hypodermic needle was reported. This was the injection of drug solutions by means of a high velocity jet projected through a micro-fine orifice. Since a needle is not used and the medicament is injected with great force through an orifice of 1/30 the size of an 18-gauge needle, there is essentially no pain. The injection technic has the additional advantage of rapidity for mass inoculation in immunization programs. Patients with apprehension about an injection by needle welcome the use of this device. Hingson *et al.* (1963) reviewed the historical development of jet injection instruments and described their experiences with 1½ million injections in parenteral therapy and in preventive medicine. The devices are known as the Hypospray, the Velodermic jet, and a multiple dose injector, the Press-O-Jet. The latter instrument can be used to inject more than 1000 patients per hour. In mass innoculation programs with typhoid vaccine, diphtheria and tetanus toxoid, Salk vaccine and smallpox vaccine, this method of injection provides the only feasible means of widespread immunization. The efficacy of jet injection appears to equal that of subcutaneous needle injection.

**Principles of intestinal absorption.** Most drugs are absorbed from the small intestine. However, evidence has been produced by Brodie and Hogben (1957) to show that many are absorbed through the gastric mucosa. The process of absorption is conditioned by: (1) the chemical nature of the drug, (2) the relative solubility of the drug in water and in lipids, (3) the diffusion of the drug through cellular membranes, and (4) the acidity or alkalinity of the substance. The gastrointestinal mucosae, similar to the plasmic membrane of a single cell, exhibit a high degree of specificity in the process of absorption. For example, glucose is absorbed three times faster than xylose. Substances like alcohol and aspirin are markedly absorbed from the stomach. The barrier between the blood and the gastric juice behaves toward drugs like a lipoid film. Weakly dissociated acids are well absorbed, whereas strongly dissociated acids are poorly absorbed from the gastric juice (Hogben *et al.*, 1959).

It is clear that large protein molecules are not absorbed from the gastrointestinal tract. Insulin, a large protein molecule, undergoes degradation by the digestive enzymes; hence it is not active when administered orally. However, epinephrine, which is a comparatively small molecule (molecular weight, 183.2) is very poorly absorbed from the gastrointestinal tract. Digitoxin, on the other hand, is a relatively large molecule, which is soluble in oil and is almost quantitatively absorbed upon oral administration. Furthermore, oil-soluble glyceryl trinitrate, which is very sparingly water-soluble, is effectively absorbed from the gastrointestinal tract.

Soluble iron salts like ferrous sulfate are readily absorbed upon oral administration. Aluminum salts do not penetrate the mucosal barrier. These examples serve to illustrate that the absorption of drugs from the gastrointestinal tract is a preferential process dependent upon many variables. The mucosal barrier does not behave like a fine sieve. Absorption is shown to be favored by oil solubility, since the mucosal barrier appears to behave like a lipoid film. Water solubility likewise favors the absorption of certain drugs. As a rule, drugs which are not appreciably soluble in either oil or water, such as barium sulfate and aluminum hydroxide, are not absorbed from the gastrointestinal tract.

Although most drugs are absorbed from the small intestine, absorption may occur from the colon. Schanker (1959) demonstrated that many drugs are absorbed from the colon of the rat by simple diffusion. His experiments indicate that



(*R. C. Adams, Intravenous Anesthesia, Paul B. Hoeber, Inc., 1944.*)

ALEXANDER WOOD
1817-1882
*The inventor of the hollow hypodermic needle*
"In all probability, what is true in regard to narcotics (when administered by the hypodermic needle) would be found equally true in regard to other classes of remedies."

the pattern of absorption of drugs from the colon is the same as that previously described for the small intestine.

The passage of a drug from the gastrointestinal tract into the circulation does not assure its penetration of the blood-brain barrier and entrance into the central nervous system. The drug may be well distributed in other organs, yet it may not enter the brain or the cerebrospinal fluid or may possibly be present in these tissues only to a very limited extent. Mayer *et al.* (1959) studied the kinetics of the passage of drugs (foreign organic compounds) into the central nervous system. Their findings are of special interest, since many drugs are intended to act upon the central nervous system, in which lie their target cells. They observed that for many drugs the blood-brain barrier and the blood cerebrospinal fluid barrier are similar, if not identical. Drugs were found to penetrate these barriers by the simple process of diffusion. The barrier is readily penetrated by lipoid-soluble drugs. Therefore, the diffusion of drugs which are ionizable appears to be dependent upon the dissociation constants and the lipoid solubility of the undissociated fraction of the compound.

**Response and method of administration.** It has been stated previously that the quantitative response to a drug depends upon its avenue of entrance to the body. The degree of response is the result of many factors. Frequently the qualitative response of a drug is modified by its method of administration.

When administered orally, insoluble bismuth salts such as the subcarbonate and subsalicylate are locally-acting protectives to the mucous membranes of the gastrointestinal tract. When injected intramuscularly, bismuth salts are treponemicides. When administered by vein, bismuth is very toxic, producing a progressive paralysis of the central nervous system. Calcium salts may be administered in very large doses by mouth. Excessive amounts will not be absorbed from the alimentary tract. By vein, large quantities of calcium salts will produce depression of the central nervous system, increased viscosity of the blood, and circulatory embarrassment.

An interesting example of qualitative change in response when the avenue of entrance to the body is varied is that of magnesium sulfate (Epsom salt). Concentrated solutions of magnesium sulfate are applied locally to swollen joints in which there is effusion of fluid. It is believed that the high osmotic pressure of the saline solution tends to draw fluid from the affected area. When magnesium sulfate is given orally in 15- to 30-gm. doses, it acts as a cathartic. The magnesium and sulfate ions, respectively, are poorly absorbed from the gastrointestinal tract. Water absorption from the tract is prevented, and the weight of its contents is increased, stimulating peristalsis and evacuation. Hence, Epsom salt is a *hydrogogue* (one which leads forth water) cathartic. The magnesium ion content of the blood is about 2 mg. per cent. If magnesium sulfate is administered by vein or intramuscularly, the magnesium content of the blood is rapidly increased. The increased concentration of magnesium ions in the blood markedly depresses the central nervous system, producing an anesthetic syndrome. In fact, magnesium sulfate solution by intramuscular injection is employed to treat eclampsia.

Previously it was stated that such drugs as insulin and epinephrine, which are potent drugs when administered parenterally, are quite devoid of activity when administered orally.

### Factors Which Modify Dosage

**Dose and body weight.** Our definition for a dose has been stated. It is *enough*. Enough to do what? To accomplish the therapeutic aim intended. But further, one poses the question—in whom? Pharmacologists give most of their doses to laboratory animals on the basis of body weight. Standard practice is to use the expression "milligrams per kilogram" or "mg./kg."

The application of this practice to clinical medicine is not always feasible, and in most cases it is not necessary. However, there are striking instances where body weight must be taken into consideration in the administration of drugs. But not only is weight important. Weight and age both are important criteria.

Official (U.S.P. or N.F.) doses are oral unless otherwise stated, and are intended for a 70-kg. (150-lb.) individual. The first problem confronting the physician with respect to dosage is the child. Obviously the dose for a child is smaller than the adult dose. But how much smaller? Certain rules have been found useful to give a *first approximation* of the dose for a child when the standard adult dose of a drug is known.

Augsberger (1962) examined the various rules that have been used for the calculation of the pediatric dose of a drug from the adult dose. Among these well established rules are Young's, $\frac{A}{A + 12}$ × adult dose, and Dilling's, $\frac{A}{20}$ × adult dose, in which "$A$" is the age of the child. It appears that no one rule can be applied with accuracy and that body surface is the most reliable criterion of calculation for children's dosage. It is a more reliable basis than body weight. It has been established that in warm-blooded animals the metabolism is proportional to the body surface. Moore (1909) assumed that drug dosages should be calculated on the basis of body area and concluded that absolute drug dosage should be proportional to the $\frac{2}{3}$ power of the body weight. Because of the difficulty of measuring body surface area, Augsberger devised a formula for calculating a child's dose from the adult dose, based upon the relationship of the age of the child (from 1 to 20 years) to body area. His formula is: $4 \times A + 20$ = the percentage of the adult dose. For example, a child 3 years old would be given $4 \times 3 + 20 = 32$, or $\frac{1}{3}$ of the adult dose. Children under 1 year of age must be considered as special dosage problems for the pediatrician, and the disease, the nature of the therapeutic agent, and the weight of the infant must be taken into consideration.

Furthermore, the child does not react like a young adult to all drugs. Children tolerate inordinately large doses of belladonna. On the other hand, their tolerance for opiates is correspondingly less than that of adults. A safe rule to follow is to calculate the dose of an opiate for a child by Augsberger's formula and then to administer half of the calculated dose. This diminished tolerance of children to opiates does not apply, however, to codeine, an opium derivative. The metabolic rate of children is higher than that of the adult. As a rule they are far more active and ingest more food per pound of body weight. These factors influence their dosage needs when they are given drugs.

Old people present another problem in dosage adjustment. Beyond the age of 70 the reduction of the average adult dose to three-quarters gives a *first approximation* of a dose for the aged. Here also there is a wide variation, because of the different degrees of debility of the aged.

**When to give another dose.** The spacing of dosage with respect to time requires judgment of the therapeutic result desired, its desired duration, the rate of absorption and excretion of the drug, and a knowledge of its metabolic fate in the body. Thus the analgesia evoked by 15 mg. of morphine has a duration of 3 to 5 hours, whereas a dose of 0.1 mg. of digitoxin will serve as a maintenance dose for a patient with congestive heart failure for 24 hours. Recently acquired knowledge of the metabolic pathways of commonly used drugs indicates that their action is frequently terminated by enzymic inactivation. The enzyme systems of the liver *microsomes* have been shown to play a dominant role in the inactivation process (Brodie *et al.*, 1958). For example, through enzymic action—oxidation, reduction, conjugation, hydrolysis, and atomic exchange within the molecule—a metabolite of the drug may be produced. The metabolite formed is quite different structurally from the parent molecule and as a rule is relatively inactive, since the process appears to be aimed chiefly at detoxification of the foreign compound. Therefore, although the metabolite of the drug molecule may enjoy a lengthy sojourn in the body prior to its excretion, the pharmacologic response may be terminated by enzymic action in a comparatively short period of time.

**Sex factors.** Women do not always respond to the action of drugs in the same manner as do men. In many instances the difference in response cannot be fully explained. Nevertheless, a knowledge of this fact is of great advantage to the prescriber. Morphine may produce more excitation prior to sedation in women than it does in men. Ephedrine frequently produces untoward symptoms in women, such as restlessness and subjective tremors of the extremities. These effects are seldom produced in men. In the medication of women, as a rule, the doses of potent drugs may be somewhat reduced. This is illustrated by the calculation of the basal anesthetic dose of tribromoethanol for the male, which is 100 mg./kg., and for the female, 75 mg./kg. The body weight of women generally is composed of a higher percentage of adipose tissue than that of men. Oxidation rates of drugs are slower in fatty tissue than in skeletal muscle and hence the effect of a drug is more pronounced and prolonged.

Evidence has been produced to show that sex hormones exert an influence on the metabolism of drugs. Quinn *et al.* (1958) observed less activity of the metabolizing enzyme system for hexobarbital in female rats than in male rats. Estradiol evoked a marked decrease in the capacity of the liver microsomal system to metabolize hexobarbital and produced a marked increase in the sleeping time of male rats.

In pregnancy the administration of drugs to the mother presents a special problem (see page 759). The placenta is not a barrier to most drugs and therefore in the administration of a drug to the pregnant woman, one must always consider the effect upon the child. Violent cathartics should be avoided because they produce pelvic congestion and griping and as a consequence may initiate abortion. Drugs that embarrass the circulation are to be avoided in pregnancy.

During menstruation increased flow and pelvic pain are produced by drastic cathartics. During lactation one must remember that many drugs are excreted in the milk. Bitter drugs excreted in the milk discourage breast-feeding. Hypnotic drugs cause depression of the infant taking the milk when they are administered to the lactating mother. There have been mass poisonings among infants who have ingested milk from cows that have eaten weeds sprayed with lead arsenate.

**Time and place factors.** The presence of food in the stomach delays the absorption of drugs. Drugs are absorbed more rapidly from the gastrointestinal tract when it is relatively devoid of food. It is a matter of common knowledge that alcohol produces a far more rapid and intensified action on the central nervous system when ingested prior to eating than it does after a meal. The reasons for this are obvious. The admixture of alcohol or other drugs with food delays absorption.

Diarrhea diminishes the sojourn of a drug in the gastrointestinal tract and reduces the fraction absorbed. During periods of protracted diarrhea, larger than usual doses of drugs must be administered orally to elicit the desired response. Emotional states which produce spasms of the sphincters of the alimentary tract, especially in the pylorus, tend to prevent the passing of the drug into the intestine. Hence absorption is delayed.

The time of the day affects the action of a drug. Daylight is a stimulant, enhancing the effect of stimulating drugs and diminishing the action of hypnotics. Darkness is a sedative. Hypnotics are more effective at night; larger doses of stimulants are required in the evening to produce their characteristic effect.

There are also seasonal variations in drug response. In hot, humid weather, when one's metabolic rate is depressed and one's resistance is lower, drugs generally produce a more pronounced effect. Oxidation and detoxification are slower and therefore the effect is intensified and of longer duration.

Furthermore, the environmental setting in which a drug is administered, in certain instances, determines the degree of response. A high altitude with concomitant low barometric pressure diminishes the capacity of the body to oxidize drugs. Hence effect and toxicity are increased.

**Emotional factors.** The constitutional emotional pattern of a patient or his emotional status at the time of drug administration may modify the response elicited. This is notably true of drugs that affect the central nervous system. This is of great significance today in the administration of the psychotropic drugs that are intended to affect the patient's mood. Lasagna *et al.* (1955) observed that chronically ill, hospitalized patients, normal subjects, and former drug addicts varied in their response to the cerebral stimulant amphetamine and the depressant morphine. Thus one observes that the effect of a drug, which is designed to produce a subjective response, is determined not only by its pharmacologic action but also by the psychogenic response of the patient to his surroundings.

Evidence of the emotional status of the patient affecting the response to drugs is illustrated by the response of patients to *placebos. Placebos are inert dosage forms, usually tablets or capsules, containing sucrose or lactose.* A placebo administered by a physician in whom the patient has confidence may upon suggestion by the prescriber be followed by striking improvement in sleep, appetite, general well-being, and bowel habits. Placebos have their place in medical practice and may be specifically indicated, along with other agents, when it is desirable to elevate the patient's threshold to pain and thus reduce the requirements for sedatives or narcotics. They provide a treatment for the patient to think about, but not to become dependent upon, however.

**Biochemical individuality.** There are many subtle personal differences that may modify an individual's response to a dose of a drug. Williams (1956) used the term *biochemical individuality* to describe the biochemical deviations which can be demonstrated to exist among all members of any biologic group. Other variations from person to person are known; these are emotional and physiologic. Therefore, it is perhaps fallacious to focus attention on a "normal man," as everyone is a deviate. Our understanding of an individual's susceptibility to disease and his response to drug therapy must be predicated upon a better knowledge of these deviations. In considering these facts it becomes obvious why mastery of the art of therapeutics requires years of clinical medical experience.

**Idiosyncrasy.** This interesting word has its etymology in the three Greek words, *idios* (one's self), *syn* (with), and *krasis* (mingle). Thus it means one mingles with himself or has a personal peculiarity. The term is employed in pharmacology to express *an extraordinary response to a drug which is different from its characteristic pharmacologic action.*

Idiosyncrasy is an unusual type of cellular response to the presence of a drug. Indeed, in a sense it might be considered as a drug allergy and comparable to the frequently experienced allergies to foods. More recently the word idiosyncrasy has been frequently replaced by the term *drug allergy*. To illustrate, in idiosyncratic individuals a small dose of quinine produces *tinnitus aurium*, or ringing in the ears. Local anesthetics produce severe toxic symptoms in certain individuals. Certain persons cannot tolerate salicylates. When these are administered to susceptible individuals, they develop a drug rash. With others the same condition obtains with the sulfonamide drugs or penicillin.

Aminopyrine produces agranulocytosis in certain susceptible individuals. Cinchophen may produce fatal hepatitis in an idiosyncratic person. Certain individuals are not depressed by hypnotic doses of the barbiturates, which ordinarily cause profound sleep. On the contrary, they are stimulated and made restive.

The mechanism of idiosyncrasy is not understood, but knowing of its existence, it is important for the physician to be ever vigilant in recognizing it. Often the patient is aware of it. He will tell the physician not to give him quinine or aspirin because experience has demonstrated that he is idiosyncratic to it. The physician will do well to heed his patient's observation, for the examples mentioned have shown the possible seriousness of idiosyncrasy.

In idiosyncratic individuals certain drugs evoke a syndrome similar to anaphylactic shock. This phenomenon is elicited by the intravenous administration of histamine and is characteristic of the response to histamine release in certain allergies. Hence the relationship of drug idiosyncrasy and *anaphylaxis* is often striking.

The phenomenon of idiosyncrasy illustrates to the prescriber of drugs the fact that *all people do not respond alike to the same drug.* Indeed, this is a truism of which the physician must be aware constantly. Even in persons with no frank idiosyncrasy there are all degrees of special tolerance and susceptibility. These concepts have been mentioned in the discussions of the patient's emotional status and biochemical individuality. To emphasize the point in therapeutics, we call the reader's attention to the ancient dictum of Heraclitus, "No one can step in the same river twice." He may walk in at the same geographical spot, but the river changes and the individual changes, even from moment to moment. We may give the same drug, but all patients are different and even the same patient varies constantly with respect to time. "Never the same river twice."

**Tolerance.** Certain individuals exhibit unusual resistance to the action of drugs. These persons are said to show *tolerance* to the drug. Tolerance may be defined as *unusual resistance to the ordinary dose of a drug.* Tolerance may be acquired by constant use of a drug, or it may be natural and is then referred to as *congenital tolerance.*

The phenomenon of tolerance depends upon at least four factors. First, a drug which is administered to an individual orally may be very poorly absorbed from the gastrointestinal tract. Hence the drug may be eliminated before a concentration sufficient for response is established in the tissues. The individual may be considered tolerant. However, such tolerance is actually a *pseudotolerance*, for it does not involve the specific cells on which the drug acts. Chronic alcoholics who have an indurated intestinal mucosa from repetitious drinking do not readily absorb food. This diminished absorption applies also to alcohol, and they are able to tolerate inordinate amounts of alcoholic beverages. This is an example of pseudotolerance.

Second, tolerance is dependent upon the rate of excretion. An effective concentration in the body tissues depends upon the rate of excretion. Persistent dysentery in an individual often presents the picture of drug tolerance. The diminished sojourn of the drug in the gastrointestinal tract reduces the amount absorbed and the patient appears to exhibit drug tolerance. Such tolerance is also a pseudotolerance and may be only of a temporary character. The rapid excretion of a drug in the urine may also confer upon the individual an unusual tolerance for the compound. This type of tolerance is illustrated with the administration of bromides. Bromide ions are depressant to the brain. They are excreted in the urine. When sodium chloride is ingested, bromide is much more rapidly excreted, and the concentration of the bromide ion in the central nervous system is promptly diminished. Hence the individual will show a tolerance to bromide. Again this is a type of pseudotolerance.

Third, the tissue cells of an individual may be capable of detoxifying a drug very rapidly. This capacity of rapid detoxification may be congenital or acquired. In either case the phenomenon is *true tolerance.* The rapid oxidation of the aliphatic side chains in the barbiturate molecules by liver cells renders these hypnotic drugs inert, and through this process of detoxification tolerance is acquired by the patient.

Fourth, the tissue cells of the body may become acclimatized to the presence of the drug and fail to respond to concentrations which are ordinarily effective. *This type of cellular acclimatization or adaptation to the presence of a drug is a true tolerance.* It is frequently encountered in the administration of drugs and often accompanied by a psychogenic component. Let us therefore consider several illustrations.

The cells of the central nervous system acquire a tolerance for alcohol. The toper enjoys a true as well as a pseudotolerance for this drug. The smoker acquires a tolerance for nicotine, which in the uninitiated individual produces symptoms of nausea and malaise. The cells of the central nervous system become tolerant to morphine. The confirmed addict functions psychically very well under the influence of the drug. Although the central nervous system becomes tolerant to morphine, the pupil, which morphine constricts, does not acquire this tolerance. Further, the gut, in which morphine produces a condition of spastic tonus of the sphincters, does not share the tolerance of the cells of the brain, and many addicts to the drug suffer from constipation throughout the period of their addiction.

When the drug is discontinued tolerance generally disappears after a time. Glyceryl trinitrate used in dynamite causes headache when its vapors are inhaled even in high dilution. The workers in dynamite factories soon acquire a tolerance to the compound and do not suffer from headache. When they are away from the factory for long periods of time their acquired tolerance is lost. When they return to work they again experience the headache.

There are some interesting examples of racial tolerance. Chen and Poth (1929) showed that although ephedrine solutions, when instilled into the conjunctival sac of the Caucasian, caused marked pupillary dilation, the eye of the Negro was tolerant. In the Negro, ephedrine is not an effective mydriatic (pupil dilator) because of a congenital racial tolerance No adequate explanation has been offered. The Eskimo ingests much fat and little carbohydrate. He can tolerate the high fat diet without acidosis.

The pharmacologist is constantly confronted with species tolerance and species susceptibility. The problem is a difficult one, for ultimately, in most instances, the results of drug action on laboratory animals must be interpreted in terms of man. Let us illustrate some interesting types of species tolerance.

The rabbit tolerates large quantities of belladonna. There is an enzyme in the rabbit's liver which decomposes atropine, the principal alkaloid of belladonna. Invertebrates tolerate massive doses of strychnine. The drug acts principally upon the central nervous axis; therefore in lower evolutionary forms its action is not pronounced. Rodents cannot tolerate the plant red squill. It produces vomiting and poisons the myocardium. Animals which are incapable of vomiting do not expel it and die from its toxicity. Use is therefore made of red squill as a rat poison. Its value as a poison is dependent upon the peculiar inability of the rodent to vomit.

Quinn *et al.* (1958) studied species variation in drug metabolism using hexobarbital, antipyrine, and aniline. The studies revealed marked differences in the rate of biotransformation in different species. For example, hexobarbital was metabolized so rapidly in the mouse that a dose of 100 mg./kg. evoked a sleeping period of a few minutes, whereas in the dog the effect of the drug persisted for several hours. Of interest is the fact that in the mouse hexobarbital is metabolized 20 times and antipyrine 60 times more rapidly than in man.

The pharmacologist often notices the phenomenon of tolerance in acute experiments. For example, if an animal is prepared for blood pressure recordings and a dose of ephedrine sulfate is injected, the blood pressure rises and remains at an elevated level for a considerable period of time. Subsequent doses, however, elicit a diminished response; ultimately the injection of the drug produces no change in blood pressure. It is believed that the agent is adsorbed on, or unites with, the receptor substance in the target cells and thus thwarts the subsequent response. This phenomenon of acute tolerance is called *tachyphylaxis.*

Tolerance is usually acquired for one specific type of chemical structure. For instance a patient who develops a tolerance for one type of barbituric acid derivative is generally then tolerant to all barbiturates. However, this tolerance does not go beyond this type of chemical constitution. Therefore, in a barbiturate-tolerant patient hypnotics of dissimilar chemical constitution such as chloral hydrate and paraldehyde may be used. In other words, the patient does not exhibit a *cross tolerance* to all hypnotics. However, the anesthesiologist is well aware of the cross tolerance which is exhibited in chronic alcoholics to the anesthetic diethyl ether. The chronic alcoholic requires inordinate amounts of ether to produce anesthesia.

**Cumulative effect.** It has been stated that tissue cells require a specific concentration of a drug before a characteristic response is elicited. Often this response is not evoked by the first dose of the drug. Perhaps two or more doses are required before the response is produced. A drug is said to have a *cumulative action when its elimination and/or catabolism are relatively slow and the full response is the result of the summation of two or more doses.* Digitalis in the treatment of congestive heart failure behaves in this manner. The development of "plumbism" or painter's colic by the repetitious impinging of lead salts on the surface of the skin and their slow elimination is another example of cumulative action. Lead salts and the salts of many other heavy metals are cumulative in their action on tissues.

Certain solvents used in industrial processes such as carbon tetrachloride and trichloroethylene evoke toxic cumulative effects in workers who repeatedly inhale even small concentrations of the vapor of the solvent. The smogs that occur in dense industrial areas often contain many toxic chemicals that are capable of producing localized cumulative effects upon the mucous membranes of the eyes and nose. Systemic cumulative effects may result from the repetitious inhalation of the vapors. The protection of industrial workers from such noxious cumulative effects of industrial chemicals as these is a major public health program.

**Synergism.** *Synergism refers to the facilitation of a pharmacologic response by the concomitant use of two or more drugs.* It is often the basis for the use of more than one ingredient in a prescription. Indeed, it is conceded by even the most critical observers in therapeutics that there are instances where two or more drugs will accomplish a therapeutic aim more effectively than any single drug. Synergism, from the Greek *ergo* (work) and *syn* (with), indicates the working together of two drugs—a pharmacologic cooperation. The total effect of two drugs may be greater than the sum of their independent actions, if their action sites or target cells are different. When the sites of action are the same, the total response is generally equal to the sum of the two actions. For example, the administration of a barbiturate and of alcohol simultaneously elicits a simple summation of sedative effect. The target cells are presumably the same. Let us consider certain common examples of synergism.

A patient has muscular pain and because of the pain cannot sleep. Aspirin is prescribed to relieve the pain and with it a barbiturate is used to produce sleep. The drugs are synergistic in this condition and together they will accomplish the therapeutic aim more effectively than any safe dosage schedule of either drug separately. The administration of a mercurial diuretic, preceded by an acidotic salt such as ammonium chloride, will produce more effective diuresis than either medicament given alone. Thus ammonium chloride synergizes the action of the mercurial diuretic. A cathartic like phenolphthalein, which acts upon the small intestine, will synergize the response of the cathartic cascara, the action of which is largely on the colon.

The aim of the physician is to treat the whole patient, and in the use of drugs the total effect may be synergistic in spite of the fact that pharmacologically the drugs employed are not synergistic. This is termed *clinical synergism.* A striking example of clinical synergism is the use of the vasoconstrictor epinephrine in a solution of procaine hydrochloride for local anesthesia. The vasoconstriction diminishes the blood supply to the area injected and thereby prolongs the time required for the dissipation of the local anesthetic. Hence the anesthetic activity is prolonged. In the treatment of peptic ulcer, the administration of an antacid, an antispasmodic, and a central nervous system sedative is synergistic therapy. However, the pharmacologic responses to the individual drugs have little in common. The judicious selection of synergistic therapeutic agents requires skill on the part of the prescriber.

**Potentiation** is a rather loosely-defined term which refers to the *administration of two drugs simultaneously which elicit a response greater than the sum of their independent actions.* There are few such examples in pharmacology. Frequently the term *potentiation* is improperly employed to describe synergism. Potentiation means "to endow with power." The drug administered is already endowed with the power to evoke its response. The simultaneous administration of two drugs does not endow either of them with additional power. It simply enhances their effectiveness. To illustrate, the administration of meprobamate will prolong the sleeping time induced by the previous administration of a barbiturate. It does not confer additional power upon the barbiturate but synergizes or facilitates its action.

The classical clinical example of potentiation is the action of morphine in patients to whom scopolamine (hyoscine) has been given. Each drug elicits a sedative action on the higher cerebral centers. In a patient to whom scopolamine is given, a small dose of morphine injected simultaneously produces more sedation than the sum of the effects of the two drugs if they were administered individually at different times. The mechanism of this effect remains obscure.

**Antagonism.** *Antagonism refers to the opposing actions of two drugs on the same physiologic system.* The use of antagonistic responses to drugs is especially valuable in the treatment of poisonings. Caffeine is a cerebral stimulant and therefore antagonizes the action of chloral hydrate, which depresses the brain. Acetylcholine stimulates the effector cells innervated by the parasympathetic division of the autonomic nervous system. Atropine blocks this action. The two drugs therefore are antagonists. Drug antagonism on physiologic systems is a very complex phenomenon. It is sometimes compared to the neutralization of an acid by a base. As a broad generalization, this comparison may be considered applicable, but in fact the conditions of antagonism are very specific. The stimulant:depressant ratio of drugs on the central nervous system varies from species to species and from person to person. The time of administration and the avenue of entrance to the body of each antagonist are factors of importance in determining the over-all result. One might expect the over-all effect of two drug antagonists to be the algebraic sum of the respective activities. This mathematical relationship can be observed when one is working with simple systems, such as an isolated smooth muscle strip. Atropine blocks the muscle contraction elicited by acetylcholine on the test object by competing with it for the *muscle-activating receptor sites.* The antagonism between the two drugs is readily subject to mathematical computation. On the other hand, this is not easily achieved clinically, and it is only from long experience and careful observation that one can empirically arrive at the proper dosage schedules of drugs which elicit antagonistic actions.

**Contraindications and side effects.** Frequently drugs are *contraindicated because of the physiologic or mental state of the patient.* Most drugs have certain well-defined contraindications with which the physician should be familiar. These may be very harmful or even fatal to the patient. For example, an asthmatic patient should not be given cholinergic agents which would cause bronchial constriction and aggravate the asthmatic syndrome. Intravenous calcium salts may be fatal to a digitalized patient, as the calcium ion synergizes the action of digitalis on the heart. Reserpine may be contraindicated for hypertension in a patient with psychopathic diathesis, for it might aggravate the mental symptoms. Phenobarbital, which is excreted by the kidney in the urine, must be cautiously administered to a patient with renal disease.

Most drugs elicit *side effects. These are drug-induced symptoms which are undesirable.* Indeed the side effects, if severe, must often be weighed against the therapeutic gain which is expected. For example, reserpine produces nasal stuffiness; aspirin often evokes tinnitus aurium and the ganglionic blocking agents used in hypertension elicit constipation. Frequently side effects disappear upon continued use of a drug, especially upon a reduced dosage schedule. Further, the patient may adjust to them and cease to be annoyed by their presence. They are always less alarming to the patient if he is told what to expect upon drug therapy by the physician.

**Pathologic conditions.** As a rule, drugs are not administered to individuals who are not ill. A disease frequently alters the response of the organism to a drug. For instance, salicylates reduce body temperature when it is elevated, but they do not reduce normal body temperature to a subnormal level. In hepatic disease certain barbiturates are slowly detoxified, and drugs such as pentobarbital produce an enhanced and prolonged action. In a patient with renal and hepatic disease the sulfonamide drugs are less rapidly detoxified and excreted, and therefore the usual dose is potentially more toxic. In a normal person 4 gm. of sodium bicarbonate will generally shift the acid-base equilibrium of the

blood and tissues to the alkaline side and cause the excretion of a less acid, cloudy urine. In the diabetic with acidosis the bicarbonate is neutralized by the beta-hydroxybutyric acid in the tissues, and the acidity of the urine remains essentially unchanged.

Having considered the methods of administering drugs and factors which modify their dose, our attention will be directed to the mechanism of drug action. The cellular response to drugs is the topic of the next chapter.

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# 8

# General Pharmacologic Principles and the Response of Cells to Drugs

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We have followed the agents used in the treatment of disease from their sources through their dosage forms to the bedside of the patient. Methods of administration and factors which modify dosage were discussed. Our next consideration is the central theme of pharmacology: how do drugs act in the treatment and cure of disease? Are there any generalizations which can be established correlating the response of living cells to drugs? One can readily appreciate the broad scope of the cellular response to drugs, including such actions as the relief of a headache with aspirin, the cure of syphilis with penicillin, and the production of surgical anesthesia with ether. In spite of the multiplicity of uses of drugs in the treatment of disease, certain broad principles of pharmacologic response have been established. These principles, applicable to all forms of medication, are the chief concern of this chapter.

## Types of Drug Action

Drugs used in the treatment of disease act on the tissues mainly in three ways. They

1. Stimulate
2. Depress
3. Irritate

In addition, drugs are used as replacement therapy and to attenuate or kill invading organisms.

Most of the agents used in pharmacotherapy may be classified under one of these headings. To be sure, the lines of demarcation among the classifications are not sharp. There is much overlapping. Frequently the character of the action refers specifically to one system of the body. Other systems may respond differently to the same drug.

The responses elicited by drugs are *quantitative* in character and not *qualitative*. A drug does not change the character of the function of a system upon which it acts. It either increases the functional activity of the system or diminishes it. This imposes marked limitations upon the use of drugs in the treatment of disease. This statement of drug action and its limitations is basic and is applicable to all drug therapy.

**Stimulation.** *Stimulation is the term used to indicate an increase in activity of specialized cells.* It is augmented function. Drugs act with remarkable specificity to augment the functions of various physiologic systems. Caffeine stimulates the activity of the brain. Strychnine increases the reflex activity of the spinal cord and produces hyperreflexia. Epinephrine stimulates the cells innervated by the adrenergic fibers of the autonomic nervous system. Acetylcholine functions as an analogous stimulant to the parasympathetic nervous system. Curare stimulates the spinal cord but depresses skeletal muscle at the neuromuscular junction. Atropine in large doses stimulates the activity of the cerebral cortex but simultaneously depresses the activity of the cells innervated by cholinergic nerves by blocking the action of acetylcholine.

It should be noted again that the pharmacologic response of stimulation is not qualitative, *i.e.*, the functional activity of the organ is not changed. It is intensified. This is most interestingly shown by the action of strychnine. As was stated, the drug stimulates the reflex activity of the spinal cord. At all dosage levels the action remains reflex. It never becomes voluntary. Unless a stimulus reaches the cord over the sensory nerves, the response is not elicited. Poulsson (1890) exposed the skin of a frog to a strong cocaine solution. The animal in this condition was then strychninized. No hyperreflexia was produced. Cocaine, which is a local anesthetic, blocked the reflex arc in the sensory nerve endings in the skin. No stimuli reached the cord.

Is there a limit to stimulation? Repeated faradic stimulation will cause protoplasmic changes that will ultimately result in a loss of function. Repetitious stimulation with drugs produces similar results. Function is lost. There is no anatomical lesion produced. However, overstimulation results in depression of functional activity. If this is true, one immediately poses the question: is not all depression the result of overstimulation?

**Depression.** *Depression is the term used to indicate a decrease in the activity of specialized cells.* It is a diminished function. Atropine depresses the activity of the cells innervated by cholinergic nerves. Is this a result of overstimulation? If one cannulates the submaxillary duct and stimulates the chorda tympani, a plethora of limpid saliva flows through the cannula. If atropine is administered in small, repeated, graduated doses, the first observable effect of the drug is reduced salivary flow. There is no preliminary stimulation and subsequent depression. By means of this and many similar experiments with other drugs, it has been shown that depression is a definite type of pharmacologic response. It is not the aftermath of stimulation.

Barbiturates depress the activity of the central nervous system. They are used as hypnotics. Trimethadione depresses the activity of the motor cortex. It is used in the treatment of the petit mal type of epilepsy. Alcohol depresses the inhibitory centers of the cerebral cortex; hence it gives rise to a freer play of the basic instincts in one's personality. Morphine depresses the cough and respiratory centers in the medulla. However, it stimulates the vomiting center located in the same area of the brain. Depression, like the stimulation elicited by drugs, enjoys a marked degree of selectivity for special cells.

Drugs may diminish or increase the rate of muscle contraction by their effect. This is notably true of the heart rate. Through its vagal action acetylcholine decreases the heart rate. This is termed a *negative chronotropic action.* By blocking the action of acetylcholine, atropine accelerates the heart beat. Its action is *positive chronotropic* in character.

**Irritation.** *Irritation is the term used to indicate the effect of a drug on the nutrition, growth, and morphology of living tissues.* It refers to the action of substances capable of producing inflammation, corrosion, and necrosis of cells. This action is nonselective for special cells. Irritation in a mild form may be used as a means of stimulating function.

Mercuric salts are irritants to the kidney endothelium. They cause tubular necrosis and functional loss of the organ. In small doses, however, this irritant action of mercury compounds is used to stimulate diuresis. Cathartic drugs such as cascara and senna irritate the mucosal cells of the gut, stimulating peristalsis and evacuation.

The irritating action produced by massive doses may be sufficient to cause intestinal bleeding, manifested by bloody stools.

Mild irritants frequently stimulate the healing of lesions and allay inflammation. Very diluted solutions of silver nitrate are used in cystitis to irrigate the bladder. They allay inflammation. Mercuric oxide in the form of an ointment is applied to the mucous membranes of the eye to stimulate healing in blepharitis.

Irritants, when applied directly to tissues in sufficient concentrations and over long periods of time, produce inflammation, effusion of fluid, ulcers, and irreparable anatomical damage. Protein molecules in the tissues are denatured, dehydrated, and decomposed by long contact with many irritant drugs. Drugs of this class are called *irritants*, *escharotics*, and *corrosives*. Silver nitrate, trichloroacetic acid, zinc chloride, caustic alkalies, and concentrated mineral acids are such drugs.

**Replacement.** *Replacement is the term used to indicate the use of organs or gland secretions (hormones) obtained from animals (or prepared synthetically) in the treatment of deficiency diseases in human beings.* Replacement is a therapy of substitution. A whole gland or its hormone is administered to the individual who is suffering from a specific glandular deficiency. Insulin in diabetes mellitus is a classic example of replacement therapy with a hormone. Thyroid powder used in the treatment of myxedema illustrates replacement therapy with a whole gland of internal secretion. The widespread use of the estrogens and androgens in gonadal insufficiency is another example of replacement therapy. The far-reaching success of this type of therapy needs no special comment. It represents one of the greatest triumphs of modern medicine. It is of interest that the organs and organ extracts of animals used as food by man can be employed in the treatment of glandular deficiency diseases in man. The products of the glands of internal secretion appear to be common to all species.

**Anti-infective drugs.** *These are drugs used to attenuate or kill invading parasites.* They were formerly referred to as *specific drugs*. They possess specific toxicity for the invading parasite. They are less toxic to the host than to the invading organism. The greater the toxicity to the parasite and the smaller the toxicity to the host, the greater is the value of the drug. This selectivity of action represents the *margin of safety* and is called the *therapeutic index*.

There are numerous examples of striking therapeutic achievements among the anti-infective drugs, such as those of chloroquine in the treatment of malaria and penicillin in the treatment of syphilis.

### GENERALIZATIONS OF DRUG ACTION

One may make certain generalizations about the types of drug activity mentioned above, which will serve as therapeutic principles. They are as follows:

1. Drugs do not restore a diseased tissue to normal integrity. They stimulate a function or depress hyperexcitability while the repair processes of nature are at work.
2. Pharmacologic agents which are obtained from organs of animals may replace secretions absent or present in insufficient quantities in man.
3. Drugs may kill or attenuate invading organisms, thus effecting the cure of a disease.

In valvular disease of the heart, digitalis does not repair the damaged organ. Through its effect on the myocardium, however, it permits the diseased organ to compensate for its mechanical disadvantage. To accomplish this, digitalis by its direct cardiac action, increases the contractile force of the heart. This is termed a *positive inotropic effect*. Antacids in the treatment of peptic ulcer do not themselves cause the healing of the ulcer. The continual use of antacids, however, keeps the gastric acid buffered and thus permits the ulcer to heal. Phenobarbital does not correct the underlying cortical dysrhythmia of epilepsy, but its repeated administration depresses the motor hyperexcitability and permits the patient to remain relatively free of seizures. Morphine does not directly assist in the wound healing of severe traumatic injuries, but it relieves pain, allows the patient to sleep, and thus facilitates the process of tissue healing.

A time-honored dictum concerning the therapeutic use of drugs is, "Drugs, they sometimes cure, they often relieve, they always console."

The question which concerns us now is how do cells respond to drugs to produce the foregoing characteristic actions? Let us therefore consider the cell upon which the drug acts.

### CELLULAR RESPONSE TO DRUGS

**The cell as a physicochemical system.** The living cell is a complex colloidal dispersion of fat, protein, and carbohydrate in water containing

certain ions. Its life is a series of chemical reactions in a dynamic steady state in a polyphasic system. It may be looked upon as a biologic device to convert foodstuffs of a high energy level to a lower energy level. The energy is required for mechanical work, neuronal activity, heat production, and synthesis of cellular constituents. To do this the cell utilizes oxygen and gives off carbon dioxide. Although the reactions within the cell obey certain physicochemical laws, it is important to realize that the life process is regulated by biologic governors such as enzymes and hormones.

Most cells live within comparatively narrow limits in their thermodynamic environment. They are thermolabile. They are sensitive to small changes in hydrogen-ion concentration. Their plasmic membranes exhibit a high degree of selectivity for ions and potential foodstuffs. The cell is not a stove that will oxidize organic matter without discrimination.

The red blood cell is impervious to sodium ions; however, it permits the ready passage of potassium ions into its structure. Chloride and bromide ions pass readily into the red cell. The plasmic membrane of the amoeba will prevent the passage of the dye eosin into its cytoplasm. If the cell is killed, the membrane becomes pervious to the passage of the dye. The plasmic membranes of fresh water protozoa will resist changes in osmotic pressure. The red blood cell cannot resist changes in osmotic pressure, except within very narrow limits.

The plasmic membrane of the cell presents a definite structure of oriented protein molecules with fat emulsified in the surface. The consensus is that an alternation of oriented lipid and protein molecules in unimolecular layers appears to be its basic structural plan. The cytoplasm of the cell also presents a definite protein mosaic. Interference with the cell membrane (by physical stress or impingement of a foreign substance, such as a drug) causes a reorientation of the arrangement of the protein mosaic in the cytoplasm. One is reminded of the parts of a jigsaw puzzle. The effects of a push of the puzzle pieces on the periphery will be manifested throughout the expanse of the puzzle. Schrödinger has cogently commented: "In contrast to a crystal, which represents a design that repeats itself, the big molecules that form the living organism are like an artistically woven tapestry; it is the design of the entire tapestry that matters, not the mere repetition of a theme."

The cell and its cytoplasm are constantly undergoing exchange of constituents. One must not consider this biologic device as merely a machine for the transfer of energy. The machine is a part of its foodstuff. The molecules in the cytoplasm, cell membrane, and nucleus are in constant exchange through synthesis with the foodstuffs of the cell. The use of tracer elements has shown this. The food of the cell today is the membrane of tomorrow and the liberated carbon dioxide of a later period. The change is continuous.

Surfaces of all kinds possess unneutralized fields of force, or free valences, that have the power of attracting and holding other molecules on their surfaces. This phenomenon is called *adsorption*. The greater the surface area exposed, the greater the degree of adsorption. Thus colloidal particles in the plasmic membrane, because of their fine state of division, present large surface areas and consequently are capable of a high degree of adsorption.

Many chemical reactions are accelerated by adsorption. Hydrogen and oxygen adsorbed on platinum black combine at room temperature to form water. Enzymes are proteins; hence in body fluids they are in a colloidal state and present large surface areas. Surface adsorption upon the colloidal enzyme particle is necessary for enzyme action. Furthermore, most of the tissues of the body are colloidal and separated by a network of membranes that exhibit enormous surfaces. It is likely that adsorption, occurring on the membrane surface, initiates many reactions that are vital and cause changes in surface tension and cellular consistency.

**The cell depressed and stimulated.** There are certain physicochemical changes which occur when cells are stimulated or depressed in their functional activity. These are shown in table 8-1.

**Oxidation in the cell.** Without oxygen, cells die. The utilization of oxygen by cells is a very complex phenomenon. It may be increased or diminished by the presence of drugs; therefore, it it important to consider the principal features of oxygen uptake of cells.

Energy is supplied to the cell by oxidation of foodstuffs. For the purpose of discussion let us consider oxidation in its broadest sense, *i.e.*, as electron transfer. There are two general classes of cellular oxidation, *cell respiration* and *fermentation*. Each involves electron transfer and each releases energy. *The change is called oxidation when oxygen is the final electron acceptor. The*

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TABLE 8-1

| Pharmacologic | Physicochemical | Colloidal |
|---|---|---|
| Phenomena occurring when cell is stimulated | | |
| Intensified function | Increase in gaseous exchange, increased metabolism which can be measured by increased $O_2$ uptake and elimination of $CO_2$<br>Lowered viscosity<br>Increased enzymic activity | Dispersion of proteins is increased |
| Phenomena occurring when cell is depressed | | |
| Diminished function | Decrease in metabolism, decrease in gaseous exchange<br>Viscosity increased, associated with lowered surface affinities and diminished enzymic activity<br>Dehydration of cell and decreased surface | Protein material undergoes decreased dispersion |

*change is called fermentation when the final electron acceptor is an organic molecule.* The term *glycolysis* is often employed to designate special types of fermentation which occur in many animal cells, *e.g.*, the conversion of carbohydrate to lactic acid in the absence of oxygen. These two kinds of oxidation-reduction reactions are common to most living cells.

The energy produced in the cell by oxidation-reduction reactions is controlled by enzymes. There are two distinct components involved when an enzyme reacts with its substrate to catalyze a chemical change in the substrate.

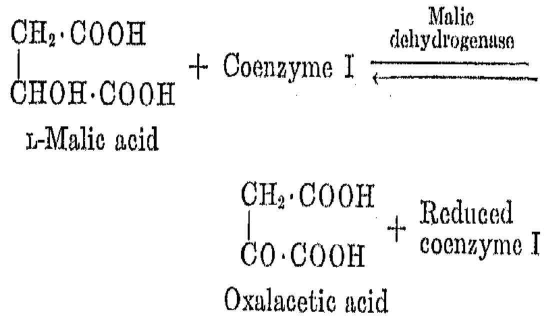
1. The combination of the enzyme with the substrate to form an enzyme-substrate complex.
2. The decomposition of the newly formed complex to liberate the enzyme and the reaction products from the substrate.

The enzyme is then free to continue the process of substrate transformation repetitiously. It should be made clear that the products of substrate reaction may be simple molecules or they may be more complicated products of enzyme substrate synthesis. An example of the first type of action is shown below, in which malic acid is dehydrogenated to form oxalacetic acid. An example of the synthesis type of enzymic action is shown on page 532, in which choline unites with active acetate to form acetylcholine. Drugs may intervene in these enzymic processes either by inhibiting or accelerating them.

Most biological oxidations may be represented by the following equation:

$$AH_2 + B \rightarrow A + BH_2$$

$AH_2$ is the foodstuff which is oxidized to A; simultaneously the substance B is reduced to $BH_2$. The oxidation is accomplished by the catalyzing action of a dehydrogenase. Dehydrogenases are usually specific for each substrate. This is illustrated by the action of L-malic acid dehydrogenase as follows:



$$\begin{matrix} CH_2\cdot COOH \\ | \\ CHOH\cdot COOH \end{matrix} + \text{Coenzyme I} \xrightleftharpoons{\text{Malic dehydrogenase}} \begin{matrix} CH_2\cdot COOH \\ | \\ CO\cdot COOH \end{matrix} + \begin{matrix}\text{Reduced} \\ \text{coenzyme I}\end{matrix}$$

L-Malic acid

Oxalacetic acid

The action of the dehydrogenase is to transfer hydrogen from the substrate to the coenzyme. Coenzyme I acts as a hydrogen acceptor by the reduction of one of the double bonds in the pyridine ring in its molecule. The reduced coenzyme is not auto-oxidizable but acts in turn as a substrate for a coenzyme dehydrogenase. For coenzyme I it is "diaphorase" and for coenzyme II it is "cytochrome reductase." Through these, hydrogen is transferred to "cytochrome."

*Cytochrome system.* Cytochromes are hemeproteins which are capable of alternate oxidation and reduction. They contain an iron atom in organic combination, which is capable of oscillating between the ferrous $Fe^{++}$ and $Fe^{+++}$ state, as follows:

$$Fe^{++} \underset{+e}{\overset{-e}{\rightleftarrows}} Fe^{+++}$$

When cytochrome is reduced it may be readily oxidized by the enzyme "cytochrome oxidase." Specific dehydrogenases may readily reduce oxidized cytochrome by transferring hydrogen from their substrates. The alternate reduction and

oxidation of cytochrome may be expressed by the following equations:

$$AH_2 + \text{Cytochrome} \xrightarrow[\text{Dehydrogenase}]{AH_2} A + \text{Reduced cytochrome}$$

$$\text{Reduced cytochrome} + \tfrac{1}{2}O_2 \xrightarrow[\text{Oxidase}]{\text{Cytochrome}} \text{Cytochrome} + H_2O$$

Thus through the cytochrome system, oxygen finally gains two electrons from two hydrogen atoms, and energy is provided for cellular function. The cytochrome oxidase provides the mechanism for the utilization of molecular oxygen in cellular respiration.

Our present knowledge of drug action on cells seems to indicate that the biological oxidation system of cellular activity is the target system for many drugs.

There are many specific oxidation-reduction systems in tissue respiration. However, as previously stated, cytochrome appears to occupy the center of the stage in aerobic cellular oxidation. Therefore special emphasis has been laid on this system. Stotz (1942) states: "Although the various substrates of respiration may require enzymes, coenzymes, and mediators, the individual pathways appear to converge at the cytochrome system. It is through the ferrous to ferric change of this system that the electrons of the ultimate substrate *hydrogen* come to terms with the ultimate oxidant, *oxygen.*"

*The drug and cellular oxidation.* The drug may be considered as a foreign substance in contact with the cell. What can the cell do with it? First, it can adsorb it on its surface. Second, it may permit the drug to penetrate the plasmic membrane and enter the cytoplasm. Third, its molecules may combine chemically with the drug to form a definite compound. This may be accomplished by chemical union of the drug with some member of an enzyme system in the cell. Let us consider three methods of cell response to drugs producing tissue hypoxia.

If carbon monoxide is brought in direct contact with hemoglobin, chemical combination occurs, with the formation of carbonylhemoglobin. Carbonylhemoglobin does not readily take up oxygen. Therefore, the oxygen transport to the tissues is blocked and cellular hypoxia results. The cytochrome system of the cell is deprived of oxygen and therefore cannot function. Cellular activity is depressed, and if the hypoxia continues, the cell will expire.

If a cyanide ion is brought in contact with living cells, let us say by human ingestion, it does not interfere with oxygen transport by the oxyhemoglobin. It, however, attacks the cytochrome system, namely, cytochrome oxidase. This enzyme is inactivated by cyanide, and oxygen is not taken up by the tissue cells from the oxyhemoglobin. The arterial blood is returned to the veins with an arterial oxygen content. The oxygen is there for use, but the drug, in this case adsorbed on the plasmic membrane, prevents oxygen utilization by its inactivation of the "mainline" oxidation system of the cell at a specific site. This site is cytochrome oxidase.

If a hypnotic drug like pentobarbital is brought in contact with living tissues by human ingestion, it does not interfere with oxygen transport by oxyhemoglobin. It does not act upon the cytochrome oxidase. The hypnotic drug acts as a depressant to the cells of the brain. It attacks the main line oxidation at some connecting link between the dehydrogenases and cytochrome reductase. With the inactivation of the dehydrogenase system, cytochrome is not reduced and as a result cannot accept the oxygen from oxyhemoglobin. Tissue hypoxia results. The action of cyanide on cytochrome oxidase is irreversible. The action of narcotic drugs on the dehydrogenase systems is freely reversible, making them available as therapeutic agents.

One of the major functions of the cell is to utilize, for the synthesis of protein, a portion of the energy acquired by the oxidative process. The precise number of protein molecules required for the functioning of a cell is not known, but it appears to be several hundred. It is possible that each of these, if not all of them, serve as enzymes, directing the multiplicity of chemical reactions that go on simultaneously within this biological unit. The synthesis of a protein molecule, containing about 200 amino acid units linked chemically in specific sequence, is directed by desoxyribonucleic acid (DNA). DNA molecules carry the genetic code of protein synthesis for the 20 common amino acids and direct their sequence in protein structure. The genetic code for each protein is carried by a particular region on the DNA molecule. It appears that at a cellular level evolutionary changes determine the code of the DNA molecule for amino acid sequence in protein synthesis (Nirenberg *et al.*, 1963). Extracts from bacterial cells, referred to as "sap," are capable of protein synthesis when provided with the code-fixing DNA and the code messenger ribonucleic acid (RNA).

This comparatively new field of investigation is of great importance in the administration of drugs. In the field of antibiotic therapy some of our most active drugs are capable of penetrating the bacterial cell, breaking its genetic code of protein synthesis, and killing the invading organism. It is likely that chloramphenicol functions in this manner as a bactericide. Drugs used in the treatment of cancer are often anti-metabolites. Handschumacher and Welch (1960) have shown that these drugs block the nucleic acid synthesis essential for protein synthesis and cell proliferation. This appears to be a problem of special significance during the early periods of gestation, when cell proliferation in the fetus is occurring at a rapid rate. The use of thalidomide as a mild hypnotic drug in pregnant women caused the births of thousands of babies with deformities (phocomelia). In all probability the drug, or one of its metabolites, was responsible for the disruption of the normal genetic code.

## THE CHEMICAL CONSTITUTION OF THE DRUG

Many drugs that depress the activity of specialized cells are not modified by the metabolic processes of the cell. They enter the body, produce their effect, and leave the body unchanged. Among these compounds are the volatile anesthetics like ether $(C_2H_5)_2O$, chloroform $CHCl_3$, nitrous oxide $N_2O$, and cyclopropane $C_3H_6$. Compounds of this character generally evoke one type of response only, namely, depression. They have a greater solubility in lipids than they do in water, hence they are partitioned into the lipids of the cell. Their presence causes a diminished oxygen uptake of the cell and therefore depresses activity. As their distribution into the lipids of the cells is a function of their oil/water coefficient, the chemical constitution of their molecules seems to play a minor role in determining the response of the tissues. It will be noted that the foregoing anesthetics show a marked variation in their chemical structures. Their common property is a high oil/water coefficient.

Based upon this property, Overton (1901) and Meyer (1899) at the turn of the century proposed a theory of narcotic action. In the main the theory holds that substances having high oil/water coefficients penetrate the lipids of cells and produce narcosis. Actually, the proposal was simply the statement of an observation. It is more accurate to refer to their theory as a hypothesis of narcotic distribution rather than of narcotic action.

Today the evidence is quite convincing that the presence of these narcotic substances in the tissue cells interferes with the cytochrome system, at some connecting link between the dehydrogenases and cytochrome reductase, producing reversible cellular hypoxia. The basic question of why this type of molecule attacks the cytochrome system at this point remains unanswered.

Although many compounds of the hydrocarbon type may enter the body and leave it unchanged, it is apparent that the central nervous system is exquisitely sensitive to their structural configurations. Thus one observes that the hydrocarbons, cyclopropane and cyclobutane, are anesthetics. However, the next member of the series, cyclopentane, produces convulsive seizures when inhaled.

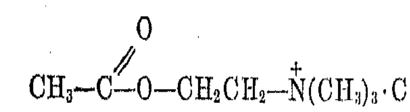
## SPATIAL CONFIGURATIONS OF MOLECULES

**Receptor sites.** There is no evidence to indicate that drugs exert their action by remote influence upon the cells of the target organ. Direct contact is necessary. It is generally conceded that the action is evoked by direct contact with the *receptor site* of the cell, located in the plasmic membrane. *The receptor site may be considered a locus on the plasmic membrane having the approximate geometric form of the molecule of the drug and being capable of attaching the molecule to its surface by adsorption or other forces.*

Generally complex molecules, especially nitrogenous compounds, either stimulate or depress cells. These actions do not appear to be dependent upon any special physical property such as solubility of the compounds. On the other hand, the response elicited appears to be dependent upon the structure of the molecule. Substituent groups play an important role. The spatial configuration of isomers is likewise of great importance. Let us give consideration to several interesting cases.

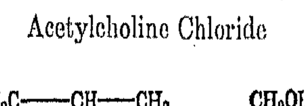
Acetylcholine stimulates the cells innervated by the parasympathetic division of the autonomic nervous system. Atropine blocks the activity of acetylcholine on the same structures. Chemically these compounds have the structures shown in the accompanying formulas.

There is no way in our present state of knowledge to predict that atropine should specifically act on the parasympathetics because of its structure. Even if it were known that atropine did act on the parasympathetics, there is no way of foretelling that its action would be depressant and not stimulating. The same holds for acetylcholine.



$$CH_3-\overset{O}{\overset{\|}{C}}-O-CH_2CH_2-\overset{+}{N}(CH_3)_3\cdot Cl^-$$

Acetylcholine Chloride



Atropine

Furthermore, without our background of knowledge, obtained by experimenting with these two drugs, one could not predict that one compound would block the action of the other. They do not combine with each other chemically to form a dissimilar substance. Yet on the cells innervated by *cholinergic* fibers, atropine and acetylcholine mutually block each other. However, at the neuromuscular junction of skeletal muscle where acetylcholine produces stimulation, atropine does not readily block this response. The reason for these specific effects on special cells is not within the boundaries of our present knowledge.

Nevertheless, the key to the solution appears to be in the spatial relationship of the radicals and atoms within the molecules. Welch and Roepke (1935) prepared and studied pharmacologically the phosphorus and arsenic analogs of acetylcholine. Their qualitative actions were like those of the parent molecule. By esterifying choline with acids other than acetic, the response evoked is essentially the same as that of acetylcholine in a qualitative sense. Quantitatively, many variants are observed. Similarly with atropine, if one modifies the structure slightly the response remains the same qualitatively, but the intensity of action changes. For example, if the tropanol nucleus of atropine is esterified with mandelic acid (phenyl glycolic acid) instead of tropic acid (*alpha*-phenyl hydracrylic acid), one obtains homatropine. The response elicited by homatropine is similar to that of atropine but weaker.

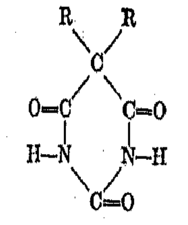
It cannot be assumed that slight changes in molecular structure will always produce compounds that will evoke similar qualitative responses. Morphine contains a phenanthrene nucleus and two hydroxyl groups. It produces profound analgesia and sleep. If the two hydroxyl groups are methylated and a second double bond is introduced into one of the phenanthrene rings, thebaine is formed. This compound retains none of the narcotic action of morphine; its action on the central nervous axis is stimulating and the compound is a potent convulsive.

The mutual antagonism between acetylcholine and atropine at the receptor mechanism of cholinergic nerves is typical of many pharmacologic responses. It is termed *competitive inhibition* or *competitive antagonism.* In competitive inhibition there is usually a structural similarity between the two components. This enables them to compete for the same receptor site on an enzyme surface. Another simple illustration of this type of reaction is the competition between oxygen and carbon monoxide for hemoglobin (see page 53). Competitive inhibition responses are, within wide limits, reversible. *Noncompetitive inhibition* results if the pharmacologic agent possesses some chemical structure which causes its reaction with the specific enzyme system to be irreversible or nearly so. It is believed that in this type of drug antagonism the two drugs combine with different parts of the receptor mechanism, so that the presence of one does not exclude the presence of the other. An example is the administration of bishydroxycoumarin, Dicumarol. This compound bears a definite structural relationship to vitamin K (see page 699). Dicumarol will produce the characteristic sign of vitamin K deficiency, *i.e.*, a lowered prothrombin level of the blood. To combat this with vitamin K, several thousand times the nutritionally required quantity of the vitamin is necessary. Indeed, if sufficient Dicumarol is administered, the prothrombin level is not elevated despite the administration of massive doses of vitamin K. The reaction becomes irreversible—non-competitive inhibition.

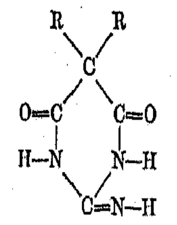
**Primary and secondary actions.** The chemical configuration of a drug molecule can be correlated directly only with the molecular changes at the *primary site of drug action.* It is not directly involved in the secondary change of events that are initiated by the primary action of the drug. For example, if a drug like neostigmine is administered, by virtue of its molecular structure it can exert a primary action at the receptor mechanism of the vagus nerve in the heart by inhibiting the activity of cholinesterase. This permits acetylcholine to accumulate and to act directly upon the myocardium, initiating a chain of secondary responses. Repolarization of the heart muscle is retarded, and a bradycardia and a drop in arterial blood pressure occurs. The carotid sinus reflexes are activated, and to compensate, the accelerator nerve to the heart elaborates epinephrine and norepinephrine at its neuromuscular junction in the heart, increasing the heart rate. The arterioles will constrict and the heart rate will increase. Thus a chain of complex circulatory events occur as *secondary actions*, sequential to the inhibition of cholinesterase as the primary action and the only effect dependent upon chemical constitution of the drug.

Let us consider further the proposition that *molecules of similar chemical configurations might be expected to evoke the same type of qualitative tissue response, subject to quantitative variations.* This generalization holds in many instances. There are, however, a sufficient number of startling exceptions to make one reticent in ever stating, with a certainty above the level of conjecture, the response expected from any compound. Let us illustrate. The aliphatic alcohols elicit a narcotic effect. The narcotic activity is a function of molecular weight. With the alcohols of high molecular weight, such as normal decyl alcohol, solubility is so small that they elicit no marked response upon cells.

Most of the common derivatives of barbituric acid with substituent groups in 5,5 positions (designated as R in the formulas) are hypnotics. Therapeutically they can be considered different forms of the same substance. Slight variations, however, in the fundamental structure of the pyrimidine nucleus annul the hypnotic response. See the formulas below:



Malonyl Urea
(hypnotic)

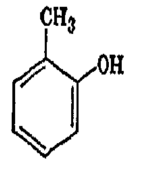


Malonyl Guanidine
(non hypnotic)

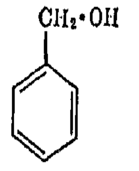
It appears therefore that the molecule of the drug must fit into a *protein template* of the micelles of oriented protein molecules on the plasmic membrane. It may be compared to a key fitting snugly into a lock. It may be likened also to the projections on the periphery of a sprocket, precisely engaging the links of a chain. A consideration of the action of isomeric compounds tends to confirm such a postulate.

**Isomeric compounds.** Certain isomeric drugs have markedly different actions on living cells. This is indicative of the important role played by the spatial relationship of the atoms in the molecule in determining the qualitative response of cells.

Consider the isomers cresol and benzyl alcohol.



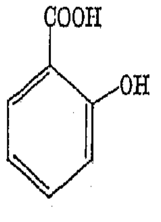
*Ortho* Cresol



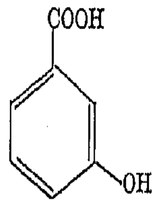
Benzyl Alcohol

Cresol is a typical phenol; it is toxic to most cells and will produce death by its action on the central nervous system. It ultimately produces a paralysis of the centers of respiration. Its principal use as a drug is dependent upon its germicidal activity. Benzyl alcohol, one of its isomers, is comparatively less toxic to all tissues. It elicits a mild antispasmodic action on smooth muscle and exhibits the properties of a local anesthetic.

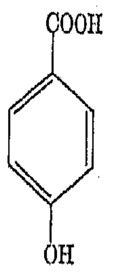
The use of the sodium salt of salicylic acid in the treatment of rheumatic fever has been established for years. The use of the salts and simple esters of salicylic acid in myalgias and headaches is widespread. But the isomeric hydroxybenzoic acids and their derivatives are useless in these fields of therapy. Their structures are shown in the formulas below.



*ortho* Hydroxybenzoic Acid
(Salicylic Acid)



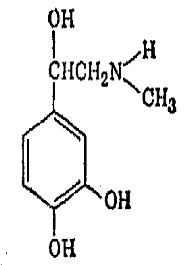
*meta* Hydroxybenzoic Acid



*para* Hydroxybenzoic Acid

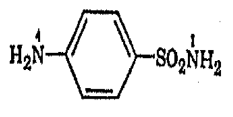
Thus the proximity of the carboxyl and hydroxyl groups to each other in space appear to be a prime factor in determining pharmacologic activity.

The *levo* isomer of epinephrine is secreted by the adrenal medulla. The *dextro* isomer, which can be readily synthesized in the laboratory, has approximately one-twelfth the activity of its *levo* isomer. It appears, therefore, that the specificity of epinephrine for the cells innervated by the sympathetics is dependent upon the arrangement of the groups on the asymmetric carbon atoms, as shown in the formula for epinephrine:

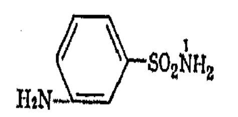


Epinephrine

Sulfonamide derivatives further illustrate the thesis of the importance of spatial relationship. The parent compound sulfanilamide is nearly useless when the substituent groups on the nucleus are changed, as shown in the formulas.

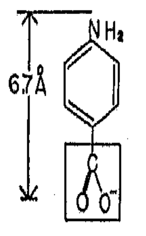


Sulfanilamide

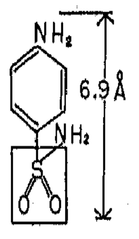


*meta* Derivative
(valueless in therapy)

It is believed that the resemblance of the basic sulfanilamide structure to *para*-aminobenzoic acid (PABA) is at least one of the factors essential for its anti-infective activity. Its *meta* derivative does not enjoy this spatial relationship to PABA. It appears that the bacteriostatic activity of sulfanilamide is dependent on the fact that it is an *isostere* of the ion of *p*-aminobenzoic acid, which is an essential metabolite in the enzyme systems of susceptible bacteria. The interatomic distances and structural relationships are shown by the formulas below.

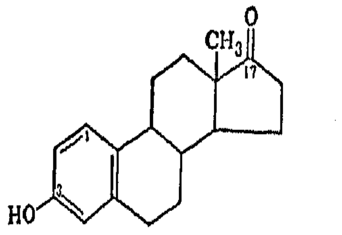


*p*-Aminobenzoate Ion



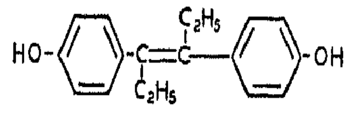
Sulfanilamide

**Spatial orientation of molecules.** It is conceivable for the substituent groups of molecules to orient themselves in space so that their structures will resemble the configuration of other compounds. Consider the structure of the female sex hormone, estrone,



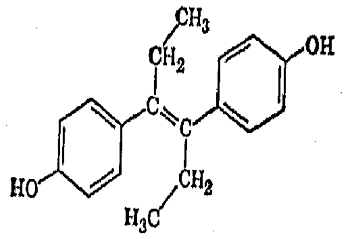
Estrone

Stilbestrol elicits estrogenic activity. It is diethylstilbestrol.



Stilbestrol

If, however, one conceives of the molecule assuming the following configuration, the similarity of the oriented molecule to estrone becomes apparent:



Stilbestrol

This lends further confirmation to our previous statement that molecules of similar configurations might be expected to evoke the same type of qualitative tissue response, subject to quantitative variations. Similar relationships in the possible orientation of molecules producing similar spatial configurations are observed in the relationship of the analgesic drugs morphine and methadon.

In pharmacologic research at present there is a definite trend toward the production of compounds which resemble important physiologic metabolites in their molecular configurations. Indeed it appears to be a most fruitful field of investigation. Changes in substituent groups and the synthesis of isosteres similar to naturally-occurring physiologic substances offer much promise for new therapeutic agents in the future. As Professor Abel so cogently pointed out in his Willard Gibbs Lecture (1927), the animal body will be the source of the most important therapeutic agents of the future.

### BIOCHEMICAL TRANSFORMATION OF DRUGS

Living cells have a remarkable capacity to modify chemically the molecules of drugs. This is often referred to as *biochemical transformation.* This is frequently achieved by the nonspecific enzymes present in the microsomes of the liver. Brodie *et al.* (1958) consider that the various oxidative pathways which are followed by the enzymes of the microsomes may all be considered hydroxylation reactions, *i.e.*, the direct substitution of a hydroxyl group for a hydrogen atom. Among the reactions which drug molecules undergo are oxidation of side chains, deamination, hydroxylation of aromatic rings, and others. A common step in microsomal oxidation appears to be the formation of an intermediate "hydroxyl" donor which, associated with a number of nonspecific enzymes, can transfer a hydroxyl group to an appropriate acceptor substrate. The purpose of the hydroxylation reactions appears to be the detoxification of the drug. For example, the drug metabolite is usually more polar than the parent molecule and therefore is less lipid-soluble. Hence, it is less capable of penetrating lipid cellular barriers and reaching the receptor site of action.

Another method of cellular detoxification is termed *conjugation.* In this process tissue enzymes are capable of esterifying the drug as sulfates and glycuronides. Amines may be acetylated and amino acid conjugates may be formed. This enzymic process affords the tissues a protective mechanism against the action of the foreign substance, as the conjugates are generally less toxic and are usually excreted as such in the urine.

## FURTHER CONSIDERATIONS OF THE ACTION OF DRUGS ON CELLS

**Evidence that drugs act on the plasmic membrane.** Many types of experiments have been conducted which indicate that often the target of drug action is the plasmic membrane of the cell. Hiller (1927) showed that if ethanol, chloretone, ether, or chloroform are injected into the cytoplasm of the amoeba, they produce no response. Similar concentrations in the environmental fluid of the amoeba immediately produce narcosis. Likewise, diluted solutions of hydrogen sulfide and cyanide, respectively, were inert when injected into the cellular cytoplasm. In contact with the plasmic membrane, however, they produced an immediate lethal effect on the cell. These simple experiments are indicative of the fact that the action of these drugs is on the cell membrane.

Cook (1926) showed that the action of a drug on the plasmic membrane was distinct from the after-penetration into the cytoplasm. Methylene blue has an atropine-like action on the frog's heart, *i.e.*, it blocks the action of acetylcholine which stimulates the receptor cells of the cardiac vagus. Its action is prompt (within 1 minute), which is indicative of action on the exterior surface of the cell membrane. Later, methylene blue penetrates the cells and dyes the heart blue. This effect, however, is apparently not associated with its plasmic membrane action. When methylene blue is removed from the perfusion fluid while the heart is still dyed intensely blue, the atropine-like action of methylene blue is obliterated.

The living organism functions largely by virtue of membranes and surface reactions. Plasmic membrane transport of ions and molecules delicately controlled by the cellular transport mechanisms is essential to normal physiologic processes. Distortion of the delicate balance by bacterial invasion, genetic defects, or degenerative processes give rise to pathologic states. Plasmic membrane transport is essential to the cells: the transport mechanisms induce an influx of essential ions and nutriments, while the plasmic membrane serves to exclude from the cell materials destructive to its vital processes. Drugs acting upon the plasmic membranes of cells can modify the transport mechanism and often restore a distorted transport mechanism to its normal state. For example, in epilepsy an abnormally high cerebral intracellular sodium ion content appears to predispose the individual to seizures. Diphenylhydantoin, used in the treatment of the disease, evokes an outflux of intracellular sodium from the brain and reduces the number and severity of the seizures. Throughout the text, in the discussions of the mechanisms of the actions of many drugs, it will be observed that the response evoked is sequential to a modification of the membrane transport system. For example, it is generally conceded that the active enzyme surface patches on cholinesterase are definitely spaced, and that one is negatively and one is positively charged. The distance is approximately the same as the distance between the positively charged nitrogen atom and the negatively charged ester linkage in acetylcholine. The nitrogen atom of acetylcholine is anchored to the negative site on the enzyme surface; the positive site simultaneously engages the ester linkage. Following the adsorption on the active patches or receptor sites, hydrolysis of the ester into choline and acetic acid occurs. Thus the concept of "exactness of fit" or "molecular complementarity" of the drug molecule upon the cell surface is emphasized.

*Active patches on the cell membrane.* Evidence of the lack of uniformity of catalytic surfaces in inanimate adsorption equilibria is well established. Active adsorbing centers have been determined on charcoal, copper, platinum, and other surfaces when these substances are used to catalyze the combining of gases.

The presence of active patches on the surface of cells has now been generally accepted. The adsorption of drug molecules on these prosthetic protoplasmic groups is one of the most plausible explanations of drug action. This view is important, as drugs markedly affect cellular activity in concentrations insufficient to form a monomolecular layer over the plasmic membrane. Then too, the difference between the activity of drugs on the cell membrane and upon the cytoplasm upon microinjection has been established.

**Strained state and enzymes.** It is likely that the drug elicits its response from the cell, as an adsorbed molecule upon the active prosthetic group of the cell's enzyme system. Modern chemical concepts state that a molecule must be converted into an active state before it is capable of reacting. Enzymes "activate" or impose a "strained state" upon their substrate molecules in the protoplasm of the cell. Pauling (1946) offers the following postulate:

> "The active region of the surface of the enzyme engages a closely-complimentary structure, not in the substrate of its normal configuration, forming what may be considered an *activated complex* for the reaction in which the enzyme is active; the strained state of the substrate decreases its activation energy to such an extent as to cause the reaction to proceed at an appreciably greater rate."

A drug that depresses or accelerates enzymic activity by plasmic membrane adsorption quantitatively influences the energy output and functional activity of the cell. It is likely in many instances that this is achieved by the presence of the drug affecting the enzyme system of the cell, causing certain enzymes to impose a "strained state" upon their substrate molecules.

Drugs with very definite and potent action elicit their effects upon cells in surprisingly low concentrations. Indeed, the concentrations are so minute that there are not enough molecules of the drug to cover more than a small fraction of the area of the cell membrane. The activity effect, therefore, appears to be confined to certain active patches on the cell surface upon which the molecules act. Let us illustrate this point.

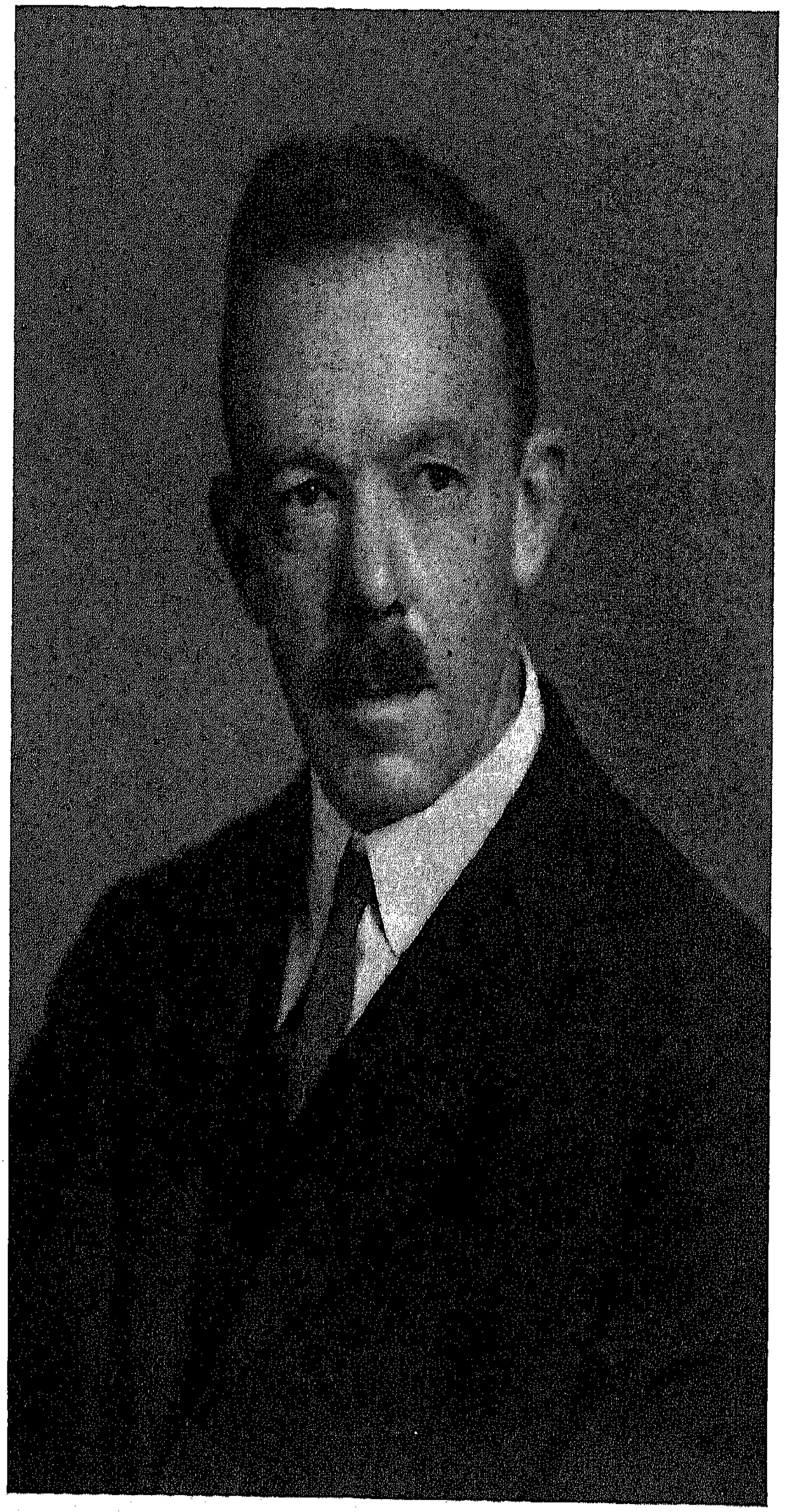
Clark (1933) gives the following interesting quantitative consideration of the action of *ouabain* on a frog's ventricle. The molecular weight of hydrated ouabain is 760; 2 micrograms of the drug contain approximately $2 \times 10^{15}$ molecules. One gram of frog's ventricle contains about $3 \times 10^{8}$ cells. In the fixation of ouabain by the frog's ventricle, 2 micrograms of the glycoside are fixed by each gram of tissue. Therefore each cell fixes about $10^{7}$ molecules. A molecule of ouabain will cover an area of about 500 sq. Å. Hence $10^{7}$ molecules cannot spread over more area than $5 \times 10^{9}$ sq. Å. The cell of the frog's ventricle has an area of $2 \times 10^{11}$ sq. Å. Therefore the ouabain adsorbed on the cell surface cannot cover more than

$$\frac{5 \times 10^{9}}{2 \times 10^{11}} = 0.025 \times 100 = 2.5 \text{ per cent}$$

of the entire surface.

Thus it is clear that a drug may elicit a response from a cell when it is present in a quantity which permits it to combine with only a small proportion of the available active patches or receptor sites. Another factor must be considered, and that is the capacity of a drug to exert its action when bound to a receptor site. This capacity of a drug is referred to by Ariëns (1957) as the *intrinsic activity* of the drug. According to this concept, a drug, to elicit a definitive response, must possess (1) the affinity for the cell receptor mechanism, and (2) the capacity to exert its action in this combined state (intrinsic activity). Accordingly, a drug may antagonize the action of a second drug by occupying nearly all of the cell receptor sites (receptor affinity) and yet exert little action of its own because of its lack of intrinsic activity.

**Membrane potential theory of drug action.** Straub's (1907) concept of the action of drugs on cells, supported later by the models of Beutner (1933), indicates that the cell membrane acts as a barrier to the drug, establishing differences in concentration in the cytoplasm of the cell and the extracellular fluid. The membrane potential established between the cell and its



ALFRED JOSEPH CLARK
1885–1941

*Distinguished investigator in the field of quantitative cellular pharmacology*

"Quantitative pharmacology must seek explanations for the phenomenon with which it deals from the laws of physical chemistry, but it must never be forgotten that the simplest living cell constitutes a system far more complex than any that would be considered worth investigating by a physical chemist."

environmental fluid is responsible for stimulation or depression.

This concept of the action of drugs acquires special significance when we consider their action on skeletal muscle. For example, the end-plate potential of skeletal muscle may be considered as a gradually decaying local depolarization of the muscle membrane. Acetylcholine, when applied to the end plate, establishes a train of propagated responses. This activity, resulting in the contraction of the muscle, has been shown to be due to the local depolarization of the end-plate locus. Curare and gallamine (Flaxedil) produce skeletal muscle paralysis, resulting from their interference with end-plate depolarization.

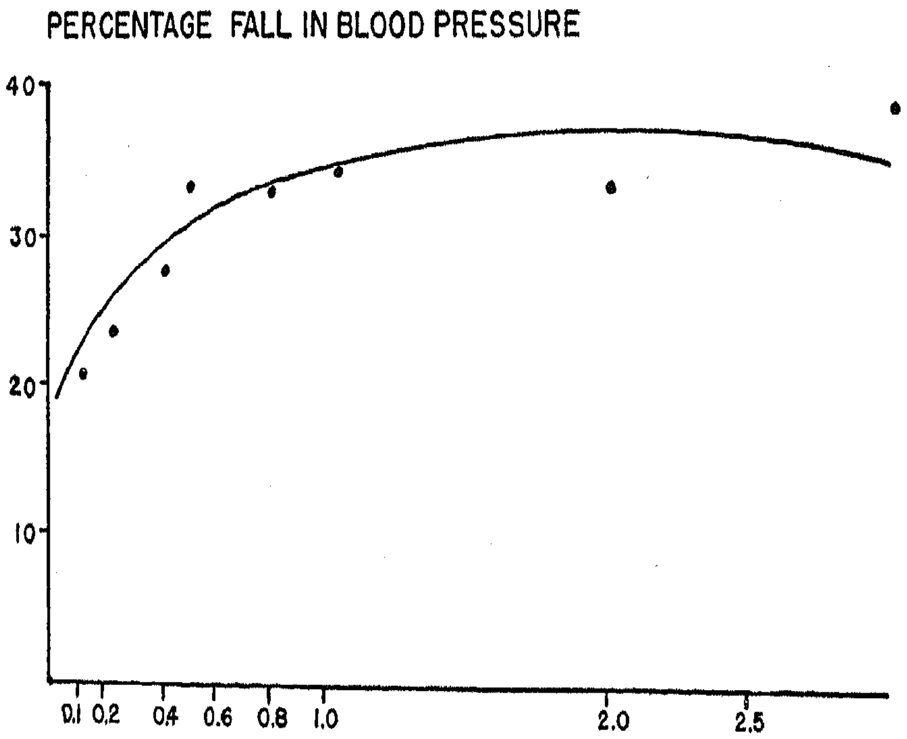


FIG. 8-1. The effect of intravenous acetylcholine upon the blood pressure of the dog. Note the exponential relationship.

Further credence to the membrane potential theory of drug activity is given by the capacity of the anti-epileptic drugs to change the brain-wave pattern and modify the cortical dysrhythmia of epilepsy. Other examples may be cited. But the point which must always be emphasized is that perhaps the membrane potential changes are simply the result of drug action and not the primary cause.

### QUANTITATIVE RELATIONS BETWEEN DOSE AND RESPONSE

**Adsorption of drugs.** Jacobs stated that the biologist was still an explorer, incapable of an accurate geodetic survey. Years ago Lord Kelvin declared: "When you can measure what you are speaking about and express it in numbers you know something about it, and when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind." Pharmacology is evolving to the stage of expressing drug action with mathematical precision. Progress is difficult indeed, but some real gains have been made.

When drugs are allowed to act upon a living tissue and the response obtained can be accurately measured, the relationship between dose and response is generally an exponential one. The response seldom varies directly as the dose. But as a rule, the response varies directly as the logarithm of the dose. Or the logarithm of dose *versus* logarithm of response may give a linear relationship.

This exponential relationship is shown by the effect of acetylcholine on the blood pressure of an anesthetized dog (fig. 8-1).

Data from many simple systems upon which drugs act, when plotted, yield a type of exponential curve which is readily adaptable to the well-known *Freundlich's Isotherm*,

$$KC^{1/n} = \frac{x}{M}$$

in which $K$ is a constant; $C$, the concentration of substance adsorbed; $n$, a constant; $x$, the quantity adsorbed; and $M$, the weight of the adsorbing substance.

In its logarithmic form the equation becomes

$$\log K + 1/n \log C = \log x - \log M$$

In true adsorption $\log x/M$ plotted against $\log C$ gives a linear relationship.

If one uses a comparatively simple biologic system, such as washed red blood cells, and studies quantitatively the adsorption of mercuric chloride on their surface, the amount of mercuric salt adsorbed follows the pattern of Freundlich's

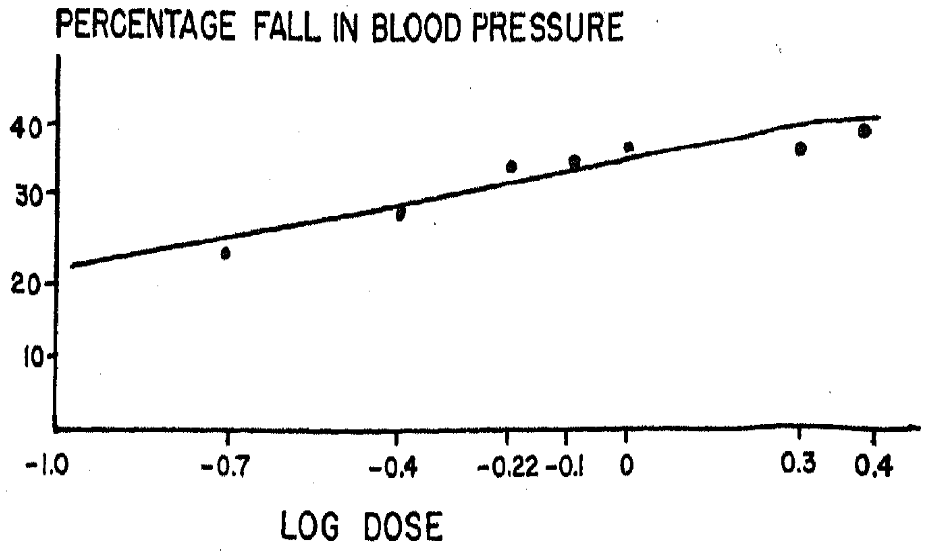


FIG. 8-2. The effect of acetylcholine intravenously upon the blood pressure of the dog: dose of acetylcholine expressed in logarithms. Note the linear relationship.

Isotherm. Likewise, the adsorption of cyanide on sea urchin eggs adapts itself to this same logarithmic relationship.

From the foregoing discussion the student of medicine might glean that efforts are being made to make our pharmacologic data quantitative. With simple systems certain well-established physicochemical patterns (Freundlich's Isotherm) are emulated. Future work will undoubtedly extend these types of measurements to more complicated living systems. For example, if one uses the data in figure 8-1 and plots the log of the dose of acetylcholine against the fall in blood pressure, the response is linear (fig. 8-2).

From the foregoing statements it is clear that adsorption on the plasmic membrane of a cell by a drug evokes a response. Chemical compound formation appears to be unnecessary. Indeed, studies have shown that there are many types of union or bonding between molecules and atoms. These may all play different roles in eliciting drug response from cells. The weakest type of bonding is the *van der Waals' bond. It is the attractive force between any two atoms of different molecules.* Van der Waals' bonding requires close proximity of atoms. The force of attraction of one such bond is small, but many of them formed by the precise fitting of a drug into its cellular receptor could constitute a significant bonding force. Hydrogen bonding, is another and a stronger type of bonding than that produced by van der Waals' forces. In biological reactions it is generally limited to the *linkage of two oxygen atoms by one hydrogen atom.* Neither of these two types of bonding is so strong as the familiar types of chemical union caused by electron transfer or electron sharing.

**Relative size of molecules and cells.** It is important to keep in mind the relatively large number of molecules present in even the smallest doses of drugs administered in the laboratory or in therapeutics. One must also consider, in the action of drugs on cells, the relative magnitude of the cell on which the molecule of the drug acts. The molecular weight of any compound expressed in grams contains 6.02 × $10^{23}$ molecules; thus 4.6 gm. of alcohol, about a teaspoonful of the liquid, contains 6.02 × $10^{22}$ molecules. A red blood cell is estimated to contain the following number of molecules:

| | |
|---|---|
| Phosphatides, cholesterol, glucose, and urea | 200 to 300 million |
| Adenosine and glutathione | 50 to 100 million |
| Potassium and chloride ions | 2000 to 10,000 million |
| Hydrogen ions | 220 thousand |

The diameter of the human red cell is 7.5 × $10^4$ Å. The diameters of small molecules are about 10 Å, of protein molecules, about 100 Å, and of Stanley's tobacco mosaic virus, 150 Å.

A knowledge of the fact that even the smallest doses administered contain a huge population of molecules enables one to understand, partially at least, why so little can do so much. As a first approximation for dosage purposes, let us take a compound with a molecular weight of 200. Then

200 gm. contains 6 × $10^{23}$ molecules
2 gm. contains 6 × $10^{21}$ molecules
2 mg. contains 6 × $10^{18}$ molecules
1 mg. contains 3 × $10^{18}$ molecules

or a milligram contains approximately ($10^9$ × $10^9$) or a billion billion molecules. It has been estimated by Parker (1930) that a 70-kg. man has about 3 × $10^{13}$ cells in his body. One milligram of the compound provides 3 × $10^{18}$/3 × $10^{13}$ = $10^5$ or 100,000 molecules available to act on each cell.

Acetylcholine in small doses causes a marked fall in blood pressure upon intravenous injection. Suppose 1.8 micrograms (6 × $10^{15}$ molecules) were injected into a 7-kg. dog (approximately 3 × $10^{12}$ cells). Then available for each cell are 6 × $10^{15}$/3 × $10^{12}$ = 2 × $10^3$ or 2000 molecules.

One of the authors (1962) perfused the coronary vessels of the isolated rabbit's heart with a solution containing 500 micrograms of glyceryl trinitrate. This evoked a 50 per cent increase in coronary flow; although only 71 micrograms of the drug was retained by the heart, the remainder appeared unchanged in the perfusate. However, on a molecular basis, the response was produced by 2 × $10^{17}$ molecules of glyceryl trinitrate.

### RECAPITULATION OF CELLULAR RESPONSE TO DRUGS

Some of the various concepts of the response of cells to drugs have been considered. It is evident that no one theory at present is adequate to cover the whole spectrum of drug action.

Physical properties play the important role among the volatile anesthetics. The cytochrome system is attacked at different strategic points by narcotics and cyanides. Enzyme systems within the cell which are affected by the presence of the drug play a major role. Chemical constitution is the dominating factor in eliciting types of response of many compounds. Adsorption according to established physicochemical laws is a factor. Membrane potentials undoubtedly are of paramount importance in interpreting certain types of drug action. The mechanism of action is very complex even in simple systems. Thus from the evidence available it is clear that the cellular mechanism of action of many drugs involves the following principles:

1. Emulating the action of a naturally-existing hormone because of a similarity in the chemical constitution, and hence eliciting a cellular response at the receptor mechanism. This is illustrated by the action of the congeners of acetylcholine, such as carbaminoylcholine chloride and bethanechol chloride, which bear a striking chemical similarity to the hormone acetylcholine.
2. Permitting an intensification of the action of a hormone by the inhibition of the action of the enzyme which decomposes it. An example of this type of response is shown in the action of neostigmine, which inhibits the enzyme cholinesterase and thus prevents the hydrolysis of acetylcholine into choline and acetic acid.
3. Blocking the receptor sites of a hormone by entering into competitive inhibition with it. Thus atropine blocks the action of acetylcholine at the receptor sites in smooth muscle cells, and curare exercises a similar blocking action at the neuromuscular junction of skeletal muscle.
4. Interfering with the metabolism of a cell by altering its metabolic pattern, usually through some facet of the main line oxidation system. Barbiturates and other hypnotic drugs apparently elicit their response through this mechanism.

These principles appear to apply also to drugs which are used in replacement therapy and in the attenuation of bacteria. Thus the hormone insulin stimulates the utilization of glucose in tissues, favorably altering their metabolic pattern. Furthermore, streptomycin kills the *mycobacterium tuberculosis* by interfering with the terminal phase of the cell's metabolic activity. Thus by a variety of mechanisms pharmacologic agents either stimulate or depress living systems.

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# PART TWO

## THE SYSTEMIC ANTI-INFECTIVE DRUGS

## 9

## *The Sulfonamide Drugs and Bacterial Infections*

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The provocative challenge enunciated by Paul Ehrlich for a *"Therapia Sterilizans Magna"* taunted chemists for fifty years in their quest for singularly nontoxic synthetic anti-bacterial chemicals. Ultimately a relatively simple organic compound was discovered to be such a chemotherapeutic agent. This discovery marked the beginning of an era, an era that has continued to the present day, and characterized by the successively improved chemotherapeutic drugs. This substance, *para-amino-benzene-sulfonamide* (sulfanilamide), was part of the molecule of an azo dye that was found to be effective in protecting mice against septicemia caused by hemolytic streptococci.

Sulfanilamide was synthesized first by Gelmo in 1906, working in the Technische Hochschule of Vienna. He published his subsequently historic paper in 1908. Gelmo was interested in dye chemistry and had no reason to investigate the bacteriological properties of the compound. According to Domagk (1936), the synthetic azo dyes had been studied for their action aginst streptococci *in vitro* and *in vivo* since 1909. Many years before 1930 Hörlein, in Germany, had found certain of these substances effective. One compound, a substituted *para*-aminobenzene sulfonamide, was observed to possess a limited therapeutic action when tested in this manner. Unfortunately, no further exploration of these drugs was made at the time.

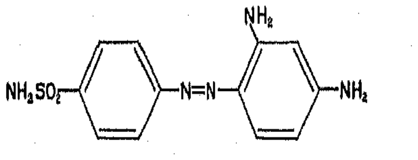
In the United States in 1919, Heidelberger and Jacobs, working at the Rockefeller Institute, observed that azosulfamido compounds containing the *p*-aminobenzene sulfonamide grouping coupled the hydrocupreine were bactericidal *in*

GERHARD DOMAGK, 1888–1964

*The investigator who discovered the anti-infective action of the sulfonamide drugs*

"Prontosil enables the mouse infected with streptococci to live if it is treated subcutaneously or orally with the drug within 24 hours of the beginning of the infection."

*vitro.* A series of investigations under the direction of Gerhard Domagk, director of the pathological laboratory of the I. G. Farbenindustrie of Elberfeld, Germany, resulted in the development in 1932 of an active compound possessing this same structure as part of the molecule. This compound was named *Prontosil*, and was patented in 1935 by Mietzsch and Klarer.

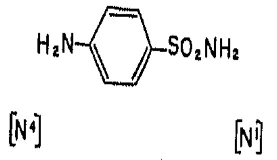


Prontosil

Prontosil was very efficacious in protecting mice against several lethal doses of *Streptococcus*

*hemolyticus* and other experimentally produced infections. Preliminary clinical trials established the value of a soluble form of Prontosil in hemolytic streptococcic septicemia.

In 1935 J. and Mme. Tréfouël, Nitti, and Bovet, working in Fourneau's (see page 923) laboratory at the Pasteur Institute in Paris, observed that in a series of azo compounds tested for their anti-bacterial activity in mice, those not possessing the *p*-aminobenzene sulfonamide grouping were inactive. These workers showed that *p*-aminobenzene sulfonamide itself was capable of protecting mice against experimental infections. They suggested that this was the active portion of the Prontosil molecule, and that sulfanilamide was formed in the animal body.



*p*-aminobenzene sulfonamide
Sulfanilamide, N. F.

Prontosil was demonstrated to be an effective anti-bacterial agent in curing experimentally infected mice inoculated with fatal doses of *Streptococcus hemolyticus.* In addition, it was active in combating human streptococcic infections. If it could be shown that *p*-aminobenzene sulfonamide, which would accomplish the same results in mice, was formed from Prontosil in the animal body, the active portion of the Prontosil molecule would be identified. Bliss and Long (1937) reduced Prontosil with cysteine hydrochloride *in vitro* and showed that the reduced material was active against hemolytic streptococcic infections and equivalent in potency to *p*-aminobenzene sulfonamide. Eventually sulfanilamide was proved to be the portion of the Prontosil molecule responsible for its anti-bacterial effects. Of equal importance was the observation that this chemical compound was relatively nontoxic in doses that were curative in experimental infections in animals and in systemic bacterial infections in man.

Tragically, the relatively simple organic chemical sulfanilamide had lain unnoticed for years in the archives of chemistry until extraordinary circumstances brought it to light. Heidelberger and Jacobs had a compound containing this grouping, but their substance was so stable that the body could not decompose it to the active form. The German workers were unwittingly successful in this regard when they synthesized an azo-linked compound that was catabolized in the body to an active form. The student of pharmacology may ponder with profit the lesson of these historic facts. The metabolic patterns of chemical compounds frequently play important functions in determining their pharmacologic effects.

With the ultimate recognition of sulfanilamide as a key anti-bacterial molecule, the way was opened for the exhaustive exploration of analogous compounds. Northey in 1948 gave an accurate tabulation of the main classes of sulfanilamide derivatives, sulfones, and related compounds that had been studied in an attempt to prepare superior chemotherapeutic agents. Over 5000 sulfonamide derivatives up to that time had been investigated. The importance of these drugs is reflected by the fact that the United States produces over 4 million pounds of sulfonamides annually.

It should be pointed out that among this class of chemical compounds other types of drugs have been discovered. The diuretics, Diamox (acetazolamide), Diuril (chlorothiazide), and related drugs may be considered as sulfonamide derivatives and are discussed in Chapter 51. The oral hypoglycemic agents Orinase (tolbutamide) and Diabinese (chlorpropamide) are sulfonylurea derivatives; they do not have the *para* amino structure. These sulfonamides are bacteriologically inert. They are considered in Chapter 54.

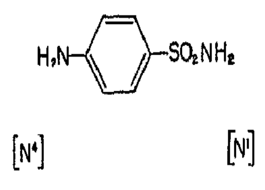
### CHEMISTRY

The basic grouping of the sulfonamides is the aminobenzene sulfonamido nucleus. Most members of the class contain the substituent groups attached through the sulfonamide nitrogen, $[N^1]$, *e.g.*, sulfadiazine and sulfadimethoxine. Other members are substituted on both $[N^1]$ and $[N^4]$, *e.g.*, succinylsulfathiazole and phthalylsulfathiazole. Sulfamylon (Marfanil) possesses singular characteristics from the standpoint of its chemical constitution. It is the only member of this class of drugs employed therapeutically in which substitution has been made between the ring and $[N^4]$. (See table 9-1.)

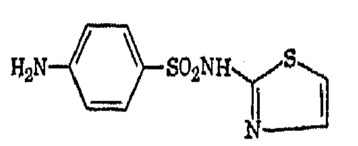
All of these drugs are white or light yellow crystalline compounds. Their solubility in water varies with the hydrogen ion concentration. Sulfonilamide and its $N^1$-monosubstituted derivatives have weak acidic properties associated with the sulfamyl group and are able to form salts

TABLE 9-1

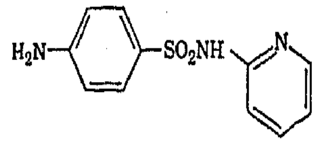
*Structure of the Sulfonamide Drugs*



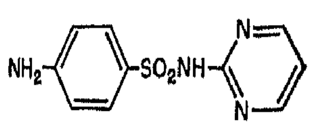
Sulfanilamide, N.F.



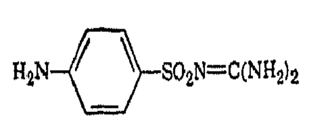
Sulfathiazole, N.F.



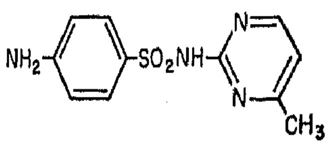
Sulfapyridine, U.S.P.



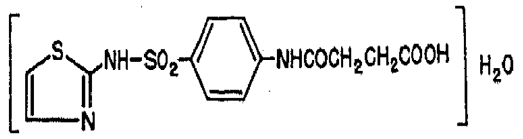
Sulfadiazine, U.S.P.



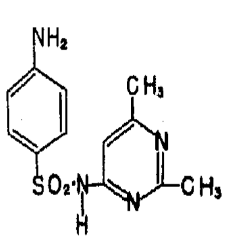
Sulfaguanidine, N.F.



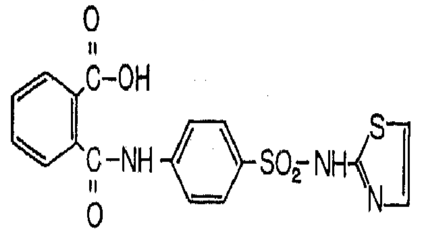
Sulfamerazine, U.S.P.



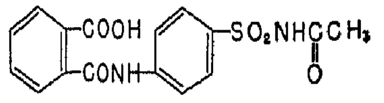
Succinylsulfathiazole, N.F.



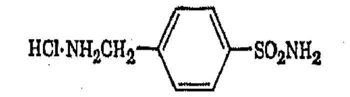
Sulfisomidine



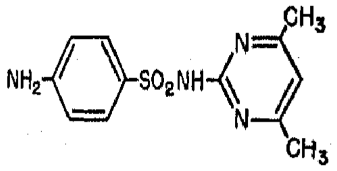
Phthalylsulfathiazole, U.S.P.



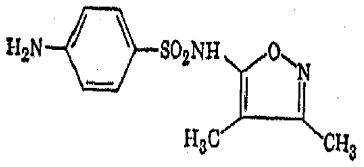
Phthalylsulfacetamide, N.F.



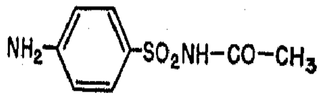
Marfanil—Sulfamylon



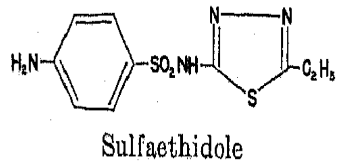
Sulfamethazine, U.S.P.



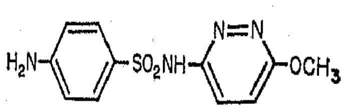
Sulfisoxazole, U.S.P.



Sulfacetamide, N.F.

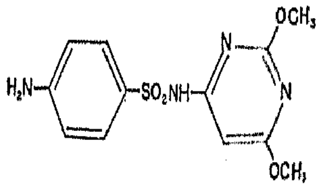


Sulfaethidole

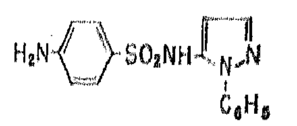


Sulfamethoxypyridazine

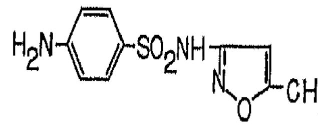
TABLE 9-1—Continued



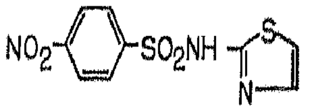
Sulfadimethoxine



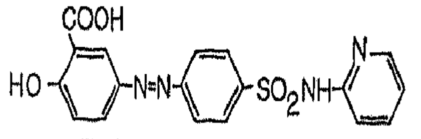
Sulfaphenazol



Sulfamethoxazole



Para-nitrosulfathiazole, N.F.



Salicylazosulfapyridine

with strong bases. Their sodium salts are very soluble in water. The sulfonamides are more soluble in human serum than in water.

The preparation of new forms of sulfonamides, *e.g.* sulfanilamidopyrimidines, sulfanilamidoisoxazoles, and their methoxy and ethoxy derivatives, has led to numerous drugs of considerable promise in anti-bacterial therapy. These drugs have a variety of actions against pathogenic bacteria, and in addition, their biotransformation in man leads to less toxic compounds.

### SURVEY OF INDIVIDUAL SULFONAMIDES

**Salicylazosulfapyridine (Azulfidine).** This sulfonamide has a special affinity for connective tissue, and it is used in the treatment of chronic ulcerative colitis. The drug is transformed in the body to aminosalicylic acid and sulfapyridine. Because sulfapyridine is toxic, special care must be exercised in the use of salicylazosulfapyridine. Drug fever, leukopenia, or exanthema indicate that the drug should be discontinued immediately. Salicylazosulfapyridine is a yellowish brown, odorless powder, insoluble in water.

The average dose for adults is 1 gm. 4 to 6 times daily. The dosage schedule should be individualized and the results of therapy carefully noted by proctoscopy.

**Sulfadiazine, U.S.P.** Sulfadiazine was synthesized by Roblin and his associates in 1940. It is a colorless or slightly yellow powder that slowly darkens on exposure to light. Sulfadiazine is soluble in water only to the extent of 1 gm. in about 13,000 ml. In general, when sulfadiazine is administered orally, adequate blood concentrations may not be reached for 4 to 24 hours. It does not enter the body fluids as readily as does sulfathiazole but it is found in the cerebrospinal fluid. Sulfadiazine and acetylated sulfadiazine are excreted readily by the kidneys.

**Sulfadimethoxine (Madribon).** This is a long-acting sulfonamide with a low renal excretion rate. It is rapidly absorbed from the gastrointestinal tract to yield a high concentration in the circulation, which is maintained for many hours. According to Boger and Gavin (1959), sulfamethoxypyridazine and sulfadimethoxine, when administered 4 times daily in a dose of 125 mg., produce increasing plasma concentrations during a 5-day period. Thus these drugs may be said to accumulate in the body, and therefore they probably attain and maintain therapeutic concentrations with a lower dosage than is the case with most of the other sulfonamides. Care must be exercised in prescribing these drugs because there is the potential danger of accumulation after excessive dosage or of unsuspected impairment of renal function.

Sulfadimethoxine appears in the urine primarily as a highly soluble glucuronide, a form more soluble than the parent substance. Its anti-bacterial activity *in vivo* is apparently only slightly inhibited by PABA.

**Sulfaethidole (Sul-Spansion, Sul-Spantab).** In the early 1940's a series of sulfanilamidothiadiazoles were synthesized and evaluated with sulfathiazole. Because most of these sulfonamides were less potent than sulfathiazole *in vitro*, they never achieved the popularity of the latter drug in the United States. Sulfaethidole, known in Europe as *Globucid*, received the most extensive clinical study. Sulfaethidole is available in the form of a liquid sustained release suspension called "Sul-Spansion."

The high solubility of sulfaethidole in body fluids and in acid urine is an advantage. It is rapidly absorbed from the gastrointestinal tract, distributed well to the extracellular fluid of the body, and less than 10 per cent is bound to the red blood cells. More than 80 per cent of a dose of sulfaethidole is excreted in the urine in 24 hours, largely in the free form.

**Sulfamerazine, U.S.P.** Sulfamerazine was synthesized by Roblin and his associates in 1940. Sulfamerazine possesses approximately the same degree of toxicity as sulfadiazine. Sulfamerazine occurs as colorless or faintly yellowish white crystals or powder, darkening slowly on exposure to light. One gram of sulfamerazine dissolves in about 6250 ml. of water at 20° and in about 3300 ml. at 37°.

**Sulfamethazine, U.S.P.** This sulfonamide was synthesized by Harworth and Rose (1943). Sulfamethazine is a colorless or yellowish powder which may darken on exposure to light. One gram dissolves in about 660 ml. of water at 29° and in 520 ml. at 37°.

**Sulfamethizole (Thiosulfil).** This sulfonamide is identical in structure to sulfaethidole except that it contains a methyl rather than an ethyl group at the 5 position of the thiadiazole ring. It is apparently a shorter-acting drug. It may be useful for administration to patients with urinary tract infections who are sensitive to other sulfonamides, since the evidence available indicates that cross-sensitization to sulfamethizole does not occur.

**Sulfamethoxazole (Gantanol).** This sulfonamide is closely related chemically to sulfisoxazole. It was introduced in 1960 for use against a wide variety of upper respiratory, urinary, and soft tissue infections. The usual adult dose is 1 gm. twice daily after an initial 2-gm. dose orally.

**Azo Gantanol** is a combination of 100 mg. of phenazopyridine hydrochloride (Pyridium) with 0.5 gm. of sulfamethoxazole.

**Sulfamethoxypyridazine, U.S.P. (Kynex, Midicel).** This sulfonamide was one of a series of sulfanilamidopyridazines synthesized by Clark *et al.* (1957). Sulfamethoxypyridazine was introduced into therapy as a long-acting sulfonamide which had the advantage of a single daily dosage. Antibacterial blood concentrations are maintained for at least 24 hours after one 2-gm. dose. Sulfamethoxypyridazine is slowly cleared by the kidneys. As it is quickly absorbed after oral doses, it is obvious that relatively high blood concentrations will be maintained for prolonged periods of time. From 82 to 96 per cent of a dose is recovered in the urine, where detectable amounts are still demonstrable for 10 to 14 days.

**Acetyl sulfamethoxypyridazine.** This is the $N^1$ acetyl derivative of sulfamethoxypyridazine. Like the acetyl form of sulfisoxazole, this form of the drug is tasteless and suitable for pediatric liquid medication. Presumably the $N^1$ acetyl form is changed in the body to the nonacetylated sulfonamide, which in turn is partly acetylated on position $N^4$ before excretion.

**Sulfanilamide, N.F.** Sulfanilamide is a colorless crystalline powder. It is odorless and is affected by light. It is soluble in water to the extent of about 1 gm. in 125 ml. The pH of a 0.5 per cent aqueous solution is 5.8 to 6.1.

**Sulfaphenazol (Orisul).** Originally used in Europe, this long-acting sulfonamide is rapidly absorbed orally and thus resembles sulfadimethoxine. Boger (1959) reported that in comparative studies sulfaphenazol produces plasma concentrations intermediate between those of sulfisoxazole and sulfamethoxypyridazine following 2-gm. oral doses, and that plasma levels were maintained above 10 mg. per 100 ml. for at least 24 hours. Sulfaphenazol is conjugated in the plasma to a limited extent (12 to 16 per cent). About 20 per cent of an administered dose is recovered in the urine within 8 hours; 30 per cent of this recovery is in the conjugated form.

**Sulfapyridine, U.S.P.,** was the first compound found to be clinically valuable, representing a $N^1$ substituted sulfanilamide. It was synthesized by Ewins and Phillips in 1938. In comparison with other sulfonamides, sulfapyridine was found to be inferior. It is irregularly and poorly absorbed. A higher percentage is acetylated in the blood and tissues, and the excretion rate is slow. These facts make sulfapyridine of historical interest only. Sulfapyridine is employed in the treatment of *dermatitis herpetiformis*. This rather rare pruritic skin disease responds favorably to daily doses of 0.5 to 1.0 gm. of sulfapyridine. In these cases the drug is not acting as an anti-infective agent; indeed the mechanism of action is obscure. At the present time sulfapyridine is the drug of choice in the treatment of dermatitis herpetiformis.

**Sulfathiazole, N.F.** This drug was synthesized by Fosbinder and Walter, and independently by Lott and Bergeim in 1939. For a time this sulfonamide was widely used.

By 1949 sufficient evidence had accumulated to indicate that approximately 18 per cent of patients who received sulfathiazole experienced untoward effects. These reactions consisted of fever, rash, acute leukemia, leukopenia, and urinary tract concretions. This high incidence of untoward reactions and the availability of less toxic sulfonamide drugs prompted the deletion of sulfathiazole from medical practice in the United States. In some countries it is still widely used.

**Sulfisomidine (Elkosin).** This sulfonamide is isomeric with sulfamethazine and differs only in the linkage of the pyrimidine ring and the positions of the two methyl groups on this ring. Meier *et al.* studied its anti-bacterial properties and introduced it into therapeutics in 1944. The substance is a colorless, crystalline powder only slightly soluble in water.

**Sulfisoxazole, U.S.P. (Gantrisin).** This sulfonamide was synthesized by Wuest and Hoffer in 1947. Sulfisoxazole is a colorless, crystalline powder. One gram is soluble in about 6,700 ml. of water. It is more soluble at pH 6 than sulfamerazine or sulfamethazine. The acetylated form is also more soluble than acetyl sulfamerazine or acetyl sulfamethazine. This makes it especially useful in urinary tract infections.

**Acetyl Sulfisoxazole, U.S.P.** Sulfisoxazole is available as its $N^1$ acetyl derivative. This is an insoluble, tasteless form of the drug. Use of this derivative obviates one of the objections to sulfisoxazole therapy, namely, the bitter disagreeable taste of the drug. This acetylation derivative on $N^1$ is not the same one that occurs in the body. In the tissues acetylation occurs on position $N^4$. In the body the $N^1$ acetyl derivative is broken down to the nonacetylated sulfisoxazole, which is the anti-bacterial form of the drug.

**Sulfisoxazole, Acetyl, Oral Suspension, U.S.P. (Lipo Gantrisin).** This dosage form contains acetyl sulfisoxazole emulsified in a vegetable oil. It is claimed to provide a higher and more prolonged anti-bacterial blood level. Five ml. are equivalent to one gram of sulfisoxazole in the form of its $N^1$ acetyl derivative.

**Sulfisoxazole Diethanolamine, U.S.P.** This salt of sulfisoxazole is soluble and is used in the preparation of injections and in various topical dosage forms.

**Azo Gantrisin.** A combination of sulfisoxazole and phenyl-azo-diaminopyridine hydrochloride is available. Tablets of this combination, providing 500 mg. of sulfisoxazole and 50 mg. of phenyl-azo-diamino-pyridine hydrochloride, are intended for oral use in the treatment of urinary tract infections. The azo dye alone has been used for many years as a genitourinary local analgesic and antiseptic (see page 215).

**Para-nitrosulfathiazole, N.F. (Nisulfazole).** This drug is a yellow, odorless, bitter powder, very slightly soluble in water. It is administered only as a 10 per cent suspension to be injected rectally.

### Sulfonamide Compounds Used Topically

**Sulfacetamide, N.F. (Sulamyd).** This sulfonamide was introduced into therapeutics as a less toxic, more soluble compound, useful in treating urinary tract infections. It was synthesized in 1939 by Crossley *et al.* in the United States and independently in Germany by Dohrn and Diedrich. Its sodium salt forms neutral solutions that may be used topically. Solutions of sodium sulfacetamide in a 30 per cent concentration instilled into the eye are nonirritating.

**Marfanil (Sulfamylon, Mesudin).** Marfanil occupies a unique place among the sulfonamides. It is the only compound of importance that has the amino group linked to the benzene ring through a carbon atom. Its anti-bacterial spectrum differs somewhat from the other sulfonamides.

Marfanil was synthesized in the United States. It was tested *in vitro*, found to be inactive, and abandoned. According to Northey (1948), the drug was investigated in Germany and discovered to be more effective against anaerobic organisms than any other sulfonamide. It was extensively used in the German army for prophylaxis against gas gangrene. Goldacre (1944) found Marfanil to be active against organisms made resistant to other sulfonamides, and found that the drug was not antagonized by PABA.

Marfanil is not employed for systemic therapy in infectious conditions, but because of its high water solubility it may be used by topical application.

### Sulfonamides Poorly Absorbed from the Gastrointestinal Tract

Certain sulfonamides are absorbed from the gastrointestinal tract only to a limited degree. While not available for systemic therapy, these compounds are nevertheless useful in treating certain intestinal disorders.

**Phthalylsulfacetamide, N.F. (Talsutin).** This sulfonamide, when administered by mouth, does not produce significant anti-bacterial blood concentrations. It is said to possess the property of diffusing into the intestinal wall. This characteristic makes it especially useful in enteric infections.

**Phthalylsulfathiazole, U.S.P. (Sulfathalidine).** An intestinal bacteriostatic sulfonamide, it acts principally upon the contents of the bowel. It is poorly absorbed from the intestinal tract, so that concentrations in the blood rarely exceed 1.5 mg. per cent. The drug is relatively nontoxic.

**Succinylsulfathiazole, N.F. (Sulfasuxidine).** This compound, like sulfaguanidine, is poorly absorbed from the gastrointestinal tract, but it is less toxic. It has the same field of usefulness as the other sparingly absorbed sulfonamides.

**Sulfaguanidine, N.F.** Sulfaguanidine was the first sulfonamide employed for the selective control of intestinal infections. It is more toxic than succinylsulfathiazole or phthalylsulfathiazole, and for this reason the drug is little used today.

This sulfonamide is relatively soluble in water and is absorbed to a considerable degree when given orally. The drug is retained in the intestine and colon and for this reason was studied as a bacteriostatic agent in bacillary dysentery.

### SULFONAMIDE SODIUM SALTS

Solutions of the sodium salts of the sulfonamides are employed for administering these slightly-soluble compounds intravenously as 5 per cent solutions in sterile distilled water or isotonic saline solution. The solutions are strongly alkaline and have a pH range of from 9 to 11. They are very irritating to tissues and may cause necrosis. In those cases in which it is desirable to obtain a high concentration of the drug promptly in the circulating blood, or in cases where gastrointestinal absorption is poor or oral administration is not possible, intravenous therapy may be employed. The availability of the rapidly-absorbed sulfonamides has decreased the necessity for intravenous therapy.

### FATE AND MECHANISM OF ACTION OF THE SULFONAMIDES

**Absorption, distribution, and excretion.** The sulfonamide drugs are absorbed from the gastrointestinal tract. The degree and speed of absorption varies. Sulfadiazine, sulfamerazine, and sulfisoxazole are essentially completely absorbed. The degree of water solubility does not necessarily determine the speed or extent of absorption of these compounds from the intestines. For example, phthalylsulfathiazole is relatively water-soluble yet it is not appreciably absorbed, while sulfadiazine, sparingly soluble in water, is absorbed.

In therapy the sulfonamides of group 1, table 9-3, may be administered on the basis of body weight, with oral doses spaced approximately 4 to 8 hours apart. For the treatment of systemic infections, this dosage schedule provides adequate blood and tissue concentrations. The sulfonamides of group 2, table 9-3, may be prescribed in one dose daily. The slow excretion of such compounds as sulfamethoxypyridazine provides effective blood levels for as long as 56 to 64 hours after an initial loading dose.

The sulfonamides are well distributed to most tissues with the exception of the brain. Certain sulfonamides appear in the cerebrospinal fluid of patients undergoing medication. The concentrations vary with the particular drug but correlate with the relative protein-binding capacity. After 24 hours of treatment, sulfadiazine in the cerebrospinal fluid has been found to average 50 per cent of the level of the nonacetylated drug in the blood. Similar values have been reported for sulfamerazine, sulfamethazine, sulfadimetine, and sulfisoxazole. In patients with meningeal infection (pneumococcic meningitis), the concentration in the abnormal cerebrospinal fluid may be much higher. In patients without meningeal infection, sulfamerazine levels in the spinal fluid have been only 10 to 17 per cent of the blood level, but in patients under therapy for meningeal infection, concentrations were observed to be from 14 to 66 per cent of that in the blood.

*Rates of absorption* after oral administration vary with the compound in question. Sulfamerazine is absorbed more rapidly than sulfadiazine. The simultaneous oral administration of equal doses of these two drugs produces a greater sulfonamide concentration of sulfamerazine than of sulfadiazine. Comparable blood concentrations are obtained with approximately one-half as much sulfamerazine as is required of sulfadiazine; however, as is the case with the other sulfonamides, the speed of absorption is not a critical factor.

After a *single* oral dose of sulfadiazine, sulfamerazine, or sulfamethazine, the urinary excretion after 24 hours amounts to 55, 27, and 30 per cent, respectively, of the dose. Because sulfamerazine and sulfamethazine are excreted more slowly, these drugs are usually administered at 6- to 8-hour intervals instead of every 4 hours.

The differences in rates of absorption and excretion play a significant role in the clinical use of these drugs. In the case of sulfamethoxypyridazine, sulfadimethoxine, and sulfaphenazole, their slow excretion rates determine the dosage schedule. *The amount of diffusible sulfonamide present in the tissues at a given blood level is the most important factor.*

*Excretion and acetylation patterns* of the various sulfonamides differ, and it is very important to keep this fact in mind. Some compounds are acetylated on the body to a considerable degree; the acetylated drug is believed to be therapeutically inactive. This $N^4$ acetylation probably occurs in the liver. Soluble glucuronides and other unidentified conjugates are excreted in the urine. The degree of glucuronide formation varies with the particular drug, but unlike the acetylated derivative, the glucuronide form is believed to be active against bacteria.

The extent of acetylation and the solubility of the acetylated form varies. The pH of the urine markedly influences the solubility of the acetylated forms, as indicated in table 9-2. Concretions and subsequent renal injury are less likely to occur with an alkaline urine. It should be pointed out that some drugs like sulfisomidine are not appreciably acetylated in the body and appear in the urine largely as the free form; hence the solubility of the acetylated derivative is not an important consideration. Those drugs that are slowly excreted and therefore require a lower dosage regimen and those that are excreted as soluble conjugates offer a decided therapeutic advantage.

Of interest is the high renal clearance of the glucuronide of sulfadimethoxine as compared with the unmodified sulfonamide. In this case the rate of excretion is determined largely by its rate of conversion to the glucuronide. This means that the duration of action of this "long-acting" sulfonamide is dependent upon the metabolic conjugation to the glucuronide. An analogous case exists for sulfamethoxypyridazine. With this drug the conversion to the $N^4$ acetylated derivative is the major controlling factor in excretion, and hence its duration of action. The renal clearance of the acetylated form in the dog is more than 10 times that of the unchanged sulfonamide (Roepke *et al.*, 1957).

It has been shown by Lehr (1944) and others that a saturated solution of a sulfonamide could still be fully saturated with a second and a third sulfonamide of different molecular structure. By using combinations of partial dosages of two or more therapeutically effective compounds, the hazard of precipitation in the urinary tract is decreased. Combinations of this type permit greater bacteriostatic activity with less danger of crystalluria.

*Rates of excretion* of the sulfonamides vary with the drug and the individual patient. Sulfadiazine and sulfisoxazole are excreted at a rate that requires spacing of doses 4 hours apart. Sulfamerazine and sulfamethazine are given at 6- to 8-hour intervals.

Sulfamethizole is administered 5 to 6 times daily. Because it is most useful in urinary tract infections, the goal of therapy is to maintain an effective concentration in the urine.

Sulfamethoxypyridazine, sulfadimethoxine, and sulfaphenazole are characterized by very slow excretion rates. For most patients single daily oral doses of these drugs may be adequate. Indeed, a more frequent dosage schedule may lead to excessive blood levels and toxic side effects.

TABLE 9-2

*Solubility of the Sulfonamides and their Acetyl Derivatives in Water at pH 5.5*

| | Solubility | |
|---|---|---|
| | Free Form | Acetylated Form |
| | *mg./100 ml.* | |
| Sulfathiazole | 98 | 7 |
| Sulfadiazine | 13 | 20 |
| Sulfamerazine | 35 | 38 |
| Sulfamethazine | 73 | 88 |
| Sulfisoxazole | 102 | 50 |
| Sulfisomidine | 169 | 8 |
| Sulfadimethoxine | 6 | 6 |
| Sulfamethoxypyridazine | 120 | 40 |

**Binding to plasma proteins.** The sulfonamides are bound to plasma proteins, chiefly to the albumin fraction of the plasma (DiCarlo *et al.*, 1963). It has been established that sulfonamide action depends upon the concentration of the unbound drug in the plasma fluid. Clinically, plasma protein binding does not offer a serious problem because the sulfonamide is gradually and easily released. However, it is necessary to remember that the "free," unbound or direct-acting sulfonamide is the form effective as an anti-bacterial agent.

Theoretically, the drug-protein combination may act as a depot tending to prevent abrupt changes in the plasma fluid level. The accepted bacteriostatic plasma levels effective against microorganisms refer to total sulfonamide concentration of both bound and free drug. Therefore, clinically the total plasma sulfonamide level is a satisfactory guide to adequate therapy. However, tissue diffusion may be determined by the degree of plasma protein binding.

The usual biochemical methods for determining blood sulfonamide levels do not distinguish between protein-bound and unbound drug. The preliminary 1:40 dilution of the blood sample releases the sulfonamide bound to the blood proteins.

Diffusion into the cerebrospinal fluid is controlled by the chemical properties of the particular sulfonamide, the concentration in the blood, and the state of the meninges. The meninges in their normal state are more selective in permitting the transfer of substances to the cerebrospinal fluid than when the barrier function is disrupted by inflammation. In the presence of infection, the cerebrospinal fluid has an increased protein content; fortunately, a higher sulfonamide concentration can be attained in the cerebrospinal fluid in an individual with meningitis than in the normal person.

The adsorption of sulfonamide drugs to blood proteins has been studied *in vitro* as a measure of the potential effectiveness of these agents in treating infections. It can be demonstrated that the drug fraction bound to plasma proteins has no anti-bacterial activity (Newbould and Kilpatrick, 1960). However, protein binding is reversible and can be utilized indirectly to maintain effective anti-bacterial concentrations of a drug that is administered only once or twice a day. Equilibrium dialysis (Clarkson and Martin, 1961) or ultracentrifugation at 63,000 to 94,500 × *g* (Sokolski, Schadewald, and Chidester, 1962) have been utilized to evaluate new sulfonamides against those drugs currently in use. The importance of these facts, together with the high intrinsic anti-bacterial activity of recently synthesized compounds, promises even more effective sulfonamides in the future.

**Mechanism of anti-bacterial action of sulfonamides.** Bliss and Long observed in 1937 that a concentration of 10 mg. of sulfanilamide in 100 ml. of serum broth inhibited the growth of a strain of *hemolytic streptococcus* in an unusual manner. The bacterial population at the end of 6 hours was the same as in the control medium; however, at about this period of time divergence in multiplication of the cocci occurred. In the presence of sulfanilamide there developed a distinct *lag of growth* of the organisms. These observations suggested a bacteriostatic action rather than a lethal effect. These workers showed by their experiment that the polymorphonuclear leukocytes played a leading role in the eventual removal of the organisms. Maher (1944), in a comprehensive review of this subject, concluded that the reticuloendothelial system was vital in sulfonamide chemotherapy. A depression of reticuloendothelial function accompanied a reduction in sulfonamide efficiency in the treatment of bacterial infections in animals. Undoubtedly, the sulfonamides exert an inhibitory action on the multiplication of the bacterial organism, but an explanation of the *therapeutic activity* of these drugs ascribes to the reticuloendothelial system a prominent role.

Domagk (1957), in reviewing the history of the sulfonamide drugs, has reiterated the importance of assessing the value of anti-infective agents by experiments on infected animals. The significance of the combined effects of host defenses and administered drug must not be overlooked in therapy.

A number of theories have been proposed to explain the mechanism of action of the sulfonamides. These were reviewed by Northey in 1948. A critical evaluation of these proposals was made by Work and Work (1948). The most plausible explanation of the inhibition of growth of bacteria by sulfonamides is known as the Woods-Fildes hypothesis.

The Woods-Fildes concept holds that *p*-aminobenzoic acid (PABA), a structural analog of sulfanilamide, is an essential metabolite for bacteria.

Stamp in 1939 prepared a concentrate from hemolytic streptococci that antagonized the action of sulfanilamide. He suggested that this material might be an essential metabolite for bacteria and an essential part of an enzyme system which was inhibited by sulfanilamide. Woods (1940) found a similar antagonist and also showed that various plant and animal tissues could serve as a source of sulfonamide antagonist. Subsequently Woods found that his concentrates contained an amino derivative of an aromatic carboxylic acid. Since competition between substances closely related chemically was well recognized in enzymic reactions, Woods tested a series of compounds related to sulfanilamide. He found that PABA inhibited the action of sulfanilamide *in vitro.* Woods suggested that PABA might be essential for the growth of those organisms susceptible to sulfonamide action. He maintained that "the enzymic reaction involved in the further utilization of PABA is subject to competitive inhibition by sulfanilamide and that this inhibition is due to a structural relationship between sulfanilamide and PABA which is the substrate for the enzymic reaction in question." Very low concentrations of PABA (from 1:5,000 to 1:25,000 that of sulfanilamide) were observed to be adequate to prevent the bacteriostatic action of sulfanilamide. Fildes at the same time suggested that the degree of susceptibility of an organism to sulfanilamide depended in part upon its ability to synthesize PABA. Thus resistant organisms were able to synthesize sufficient PABA to antagonize all the sulfanilamide present in their medium.

Disclosure of the chemical nature of folic acid as consisting of a pteridine ring, PABA, and glutamic acid moieties suggested that the sulfonamides might interfere with either the synthesis or utilization of this essential bacterial growth component. It was soon demonstrated that sulfonamides inhibited not only folic acid synthesis by susceptible strains of microorganisms but also the synthesis of pantothenic acid. Apparently sulfonamide-susceptible organisms are unable to incorporate PABA into the synthesis of pteroylglutamic acid (folic acid). Thus those microorganisms that do not require folic acid for growth or can use folic acid formed from some other source (*e.g.,* tissues) are insensitive to the action of sulfonamides.

Subsequent work has shown that susceptible bacteria need PABA for synthesizing the essential cofactor, tetrahydrofolic acid, a sequence blocked by sulfonamides. It has also been established that mammalian cells use a different metabolic route. Thus these drugs block an enzyme system present in invading cells but not present in host cells.

The following points seem to be well established:

1. PABA plays some vital function in the growth and cellular metabolism of some bacteria.
2. There is good evidence that in some cases sulfonamide-resistant organisms do synthesize PABA in greater amounts than their parent strains.
3. PABA is unique in that it is capable of antagonizing completely the bacteriostatic effect of sulfonamides over a wide range of concentration.

The theory of competitive inhibition holds only for those sulfonamides with a free amino group in the para position to a sulfonic acid or other acidic group. As pointed out previously, compounds in which the primary amino group is not aromatic may be bacteriostatic but are not antagonized by PABA.

The bacteriostatic inactivity of the isomers of sulfanilamide and its derivatives, as well as the lack of antagonism by isomers of PABA, correlate well with the Woods-Fildes theory of competitive inhibition.

The basic concept of competitive inhibition evolved by the studies with the sulfonamide drugs has offered the organic chemist and the pharmacologist an opportunity for synthesis and investigation that has had many ramifications. It has provided a valuable stimulus for the study of many general theories of drug action.

Substantial evidence has been obtained that another mechanism of action may be utilized in inhibiting bacterial growth. Fisher and Doub (1959) observed the antibacterial potency of a series of dihydro-s-triazines against medically important bacterial pathogens. Dihydrotriazine (1-(3′:5′-dichlorophenyl)-2:2-dimethyl-4:6-diamino-1:2-dihydro-s-triazine) was inhibitory to bacterial growth *in vivo* and did not act directly on known PABA-folic-folinic acid systems. There was a marked synergistic effect when dihydrotriazine was combined with sulfamethoxypyridazine. There have been few clinical reports on the value of the combination; however, it appears that it may be possible to kill pathogenic bacteria by using drugs that attack the metabolic pathways of the cell at different points.

**Bacterial adaptation to sulfonamides.** The problem of resistance of bacteria to the sulfonamides is of clinical significance. It was first encountered a few years after the advent of the sulfonamide treatment of gonorrhea. A sharp drop in the cure rate was accompanied by the isolation of an increasing number of sulfonamide-resistant gonococci. Experience has shown that as a result of successive exposure to sulfonamides an initially sensitive organism can become resistant. Under suitable conditions a bacterial organism may develop the capacity to metabolize substances which were previously toxic to it.

Two types of drug resistance must be considered. One type involves the rapid development of an enzyme pattern without cell division. Thus during metabolism of the cell, in the presence of the drug, an enzyme pattern is encouraged which permits an alternative pathway of energy utilization. A variety of bacterial species may promptly become relatively insensitive to the effects of a given drug. This has been termed *variation by enzyme adaptation.*

Another type of adaptation leading to drug resistance is brought about much more slowly. This type of resistance can be demonstrated over a series of generations of the bacteria and represents a much slower alteration in metabolic pattern. It is referred to as *variation by selection.* The change is occasioned by a slow process of selection of variants which may have a different enzymic pattern from the parent cells. These cells are better suited to the new environment; they grow and multiply and eventually are present in preponderant numbers. The other cells succumb to the action of the drug. Such drug resistance may be retained or may be lost slowly over a period of time representing successive generations. For *S. aureus* and *E. coli*, mutations occurring in random fashion give rise to resistant variants which are then favored by the presence of the drug. Such a phenomenon requires successive steps, each one yielding a greater number of resistant organisms.

Since multiplication and growth of microorganisms is a predominant factor in the development of a resistant strain, clinically every effort should be made to reduce the total number of growing organisms. Reduction in cell division diminishes the probability of mutation. Adequate blood and tissue concentrations insure satisfactory bacteriostatic activity. This is of great importance early in therapy.

From the clinical standpoint it is important to bear in mind that *bacterial resistance* to the sulfonamides differs from susceptibility of the host to the drug. Further, resistance as it is related to adaptation differs from the well-known resistance of gram-negative organisms to sulfonamides. Finally, it should be noted that there is a varied *inherent* degree of susceptibility to anti-bacterial drugs possessed by different strains of the same organism. These factors determine the initial selection of the drug of choice in therapy and are not related to the subsequent development of drug resistance.

Millar *et al.* (1963) noted that after using sulfonamides for 24 years as a specific prophylaxis against meningococcal infections, a group of B strain *Neisseria meningitidis* was isolated from a group of Navy recruits who had either recovered from the clinical symptoms of meningitis or who had been healthy carriers of the organism. They noted that in the preceding two years mass prophylaxis with sulfadiazine failed to check the occurrence of new cases of the disease. Subsequently, it was shown that *in vivo* and *in vitro* resistance to sulfadiazine could be demonstrated in the organisms obtained by cultures taken from the throats of young men either before or after sulfonamide therapy. This observation serves as a warning to the physician that he should not assume bacterial sensitivity to anti-bacterial agents even though the variety of microorganism is considered susceptible, based upon the classical picture of the clinical infection. It appears that there is no substitute for bacteriologic identification of the organism and its drug susceptibility.

### Therapeutic Use of the Sulfonamides

The sulfonamides exhibit a wide anti-bacterial spectrum. It is, however, desirable to know what organism is responsible for an infection and to determine whether or not it is sulfonamide-susceptible. The intelligent use of these drugs is dependent upon precise bacteriologic information. The drug of choice may be selected after a consideration of rate of absorption and excretion, tissue and body fluid diffusibility, and relative toxicity. The infectious diseases in which the sulfonamides have been employed successfully are set forth in table 10-2, page 93.

Sulfadiazine, sulfamerazine, sulfamethazine, sulfisoxazole, or sulfadimetine have been the sulfonamides most frequently prescribed because of their effectiveness in a wide range of common infections, their comparatively low toxicity, and the ease with which high blood levels are maintained. The introduction of sulfisomidine, sulfamethoxypyridazine, sulfadimethoxine, and sulfaphenazole, characterized by excellent absorption, slow urinary excretion, a low order of acetylation, and high solubility of the excretion products, has provided a better type of sulfonamide therapy.

Finally, because sulfadiazine appears to diffuse into the spinal fluid more efficiently, it is the drug used for certain meningeal infections. In severe infections of this character the drug is usually administered intravenously.

Recognizing that there are wide differences of opinion concerning the arbitrary selection of a drug for a disease, an attempt has been made in table 10-2 to indicate whether a sulfonamide drug or an antibiotic is the choice in the treatment of a number of bacterial infections.

Simultaneous administration of a sulfonamide and an antibiotic is not contraindicated. Full therapeutic doses of both drugs may provide more satisfactory therapy than either alone.

The sulfonamides are of no value against the viruses that initiate influenza and the common cold. Opinions differ regarding their value in preventing complicating infections by bacteria in these conditions.

**Blood concentration.** To be effective the sulfonamides must be present in sufficient concentration in the blood and tissues. Too high a blood level leads to toxic manifestations, inadequate blood concentrations, and unsatisfactory clinical response. Blood analyses are desirable during a course of therapy to insure optimal blood levels. A number of methods have been devised for determining the blood concentrations of the various sulfonamides. The method described by Bratton and Marshall (1939) is widely used. With the less toxic sulfonamides, blood sulfonamide determinations may not be necessary. Especially is this true when the clinical response of the patient is satisfactory. On the other hand, when the infection is not rapidly brought under control, or when renal function is impaired, the blood level may be helpful in determining subsequent dosage.

Some misconceptions exist regarding the "free" and acetylated sulfonamides. The Bratton and Marshall method assays free drug and glucuronides. The expression "total sulfonamide" includes $N^4$ acetylated sulfonamide in addition to free drug. The total sulfonamide level assay involves a preliminary acid hydrolysis not normally carried out in the routine determination (see binding to plasma proteins, p. 74).

According to Boger (1959), there is need for a critical appraisal of the blood levels and dosage schedules required for effective treatment. The general statement that a blood level of 10 to 15 mg. per 100 ml. is required is not necessarily true for the long-acting sulfonamides. These drugs maintain a blood concentration at a high level without toxic effects for long periods following a single dose. In addition, values of *plasma* concentration are often reported; these are approximately twice "blood levels."

**Toxicity.** The toxic manifestations noted in the course of sulfonamide therapy are generally unpredictable. Hypersensitivity to these drugs is commonly encountered and may not appear until the compound has been administered for relatively long periods of time (from several days to weeks). Usually the idiosyncrasy is manifested as a dermatitis or as a drug fever. Experience has indicated that in those individuals who become hypersensitive to the drug and who take a second course at a later date, the symptoms of hypersensitivity appear earlier and may be more severe.

Nausea, vomiting, dizziness, drug fever, and skin rash are commonly observed in patients under sulfonamide therapy. Mental disturbances have been described, and vague peripheral neuritis is sometimes encountered.

More serious toxic effects produced by the sulfonamides are cyanosis, leukopenia, granulocytopenia, and agranulocytosis with acute to mild hemolytic anemia, hematuria, and severe kidney damage. In current medical practice these severe reactions following modern sulfonamide therapy are rare. Less toxic drugs and the use of sulfonamide combinations have decreased the incidence of untoward effects.

There is evidence that the acute hemolytic anemia that follows the administration of sulfanilamide may be related to an intrinsic defect of the red blood cell, a defect that is rare among Caucasians but occurs in about 10 per cent of American Negroes. A number of aminoquinoline and aniline derivatives produce this sensitivity response in susceptible individuals with this genetically transmitted red cell defect. This type of drug sensitivity is discussed on page 155 in connection with the toxicity of the antimalarial drug, primaquine.

The exact mechanism of the production of sulfonamide cyanosis is unknown, although in part it is related to the production of methemoglobin in the blood. Methemoglobinemia alone is not considered an indication that the treatment should be discontinued.

The skin rashes from this type of therapy are sometimes the result of photosensitization of the skin. Patients receiving sulfonamides should not receive ultraviolet irradiation or prolonged exposure to direct sunlight.

Acidosis may be produced by sulfonamide therapy with sulfanilamide but does not follow the use of modern sulfonamides. Nevertheless, it may be good therapeutic practice to administer sodium bicarbonate during a course of treatment.

The formation of drug concretions and renal parenchymal cell injury have been discussed previously. The appearance of hematuria indicates that large quantities of water should be administered to solubilize the drug and to combat the dehydration that encourages crystallization in the urine.

**Oral dosage and administration.** In general two groups of sulfonamides can be recognized (see table 9-3). One group is administered in larger initial doses, with subsequent doses required at 4- to 6-hour intervals. The other class of sulfonamides is given in smaller initial doses; only one

TABLE 9-3

*Oral Adult Dosage Schedules for the Sulfonamides*

| | Initial Dose | Subsequent Dose | |
|---|---|---|---|
| | | Amount | Interval |
| | *gms.* | *gms.* | *hrs.* |
| Group 1 | | | |
| Sulfadiazine | 4 to 6 | 1 to 1.5 | 4 |
| Sulfamerazine | 3 to 4 | 1 | 8 |
| Sulfamethazine | 3 to 5 | 1 | 6 |
| Sulfisoxazole (Gantrisin) | 4 to 6 | 1 to 2 | 4 |
| Sulfisomidine (Elkosin) | 4 to 6 | 1 to 2 | 4 |
| Group 2 | | | |
| Sulfamethoxazole (Gantanol) | 1 to 2 | 1 | 12 |
| Sulfamethoxypyridazine (Midicel, Kynex) | 1 to 2 | 0.5 | 24 |
| Sulfadimethoxine (Madribon) | 1 to 2 | 0.5 to 1 | 24 |
| Sulfaphenazol (Orisul) | 1 to 3 | 1 | 24 |

dose per 12- to 24-hour period is required to maintain the blood level of sulfonamide.

The dosage depends upon the type and severity of the infection. The doses given in table 9-3 are for acute bacterial infections. However, optimal blood levels are necessary for adequate therapy. As these are determined by the individual absorption, conjugation, and excretion patterns, one must know these characteristics for each sulfonamide or class in order to use these drugs correctly. Indeed, these biochemical factors determine the dose, blood-level, and, indirectly, the toxicity of these drugs.

The dose calculation for children with severe infections is 100 to 150 mg./kg., with subsequent doses of one-fourth the initial dose every 4 to 8 hours for drugs of group 1, table 9-3. For the longer-acting sulfonamides of group 2, the usual dose for children is 2 gm. initially, followed by 1 gm. every 24 hours. Special schedules are available for infants.

In the treatment of urinary tract infections largely caused by gram-negative bacilli, sulfisomidine is given in 1-gm. doses every 8 hours; sulfisoxazole is administered in the usual antibacterial course. In these cases the dose schedule is continued until the urine cultures have been sterile for at least 3 days. The long-acting sulfonamides appear to be excellently adapted to the treatment of urinary tract infections; for this purpose they are administered in the doses given in table 9-3. Sulfamethizole is apparently useful in urinary tract infections caused by bacteria amenable to sulfonamide therapy. The usual adult dose is 0.5 gm. 5 or 6 times a day. However, lower doses have been used with satisfactory results.

*Intravenous* administration of the sodium salts of the sulfonamides has been mentioned previously. Because oral administration permits rapid absorption of the drug, there is little need for intravenous injection. However, in comatose or critically ill patients the intravenous route may be employed. Sodium sulfadiazine and sodium sulfamerazine are the sulfonamides most frequently employed in this manner. The sodium salt of sulfadiazine is administered to severely ill patients on a body weight basis: 0.1 gm./kg., with a maximum of 5 gm. at a single dose. Subsequent doses, if required, are calculated on the basis of from 0.03 to 0.05 gm./kg. of body weight. Sodium sulfamerazine is administered on the basis of 0.05 gm./kg. of body weight, with subsequent doses based on 0.025 gm./kg. of body weight. Sulfisoxazole diethanolamine is a dosage form suitable for slow intravenous or intramuscular injection. The dosage should not exceed that employed orally. Special precautions must be observed when this drug is administered parenterally.

**Therapy with sulfonamide combinations.** A mixture of two or three sulfonamide compounds has been shown to be appreciably safer than one drug alone. Animal experiments have indicated that the toxicity of three drugs in combination is less than the same total dosage of a single compound.

Clinical and experimental studies established the value of sulfonamide mixtures from the standpoint of renal protection. While it is still necessary to maintain a urinary output of 1500 ml. per day in patients receiving sulfonamide therapy, the hazards of crystalluria are reduced under triple sulfonamide medication.

Most combinations of three sulfonamide drugs are composed of closely related chemical compounds. A frequently prescribed combination is composed of equal parts of sulfadiazine, sulfamerazine, and sulfamethazine. The total daily dosage is the same as the dose that would be used if only

one of these sulfonamides were administered. With the discovery of the long-acting sulfonamides that are excreted as soluble degradation products, there is little need for sulfonamide mixtures.

**Bacterial chemotherapy of the intestinal tract.** Succinylsulfathiazole or phthalylsulfathiazole are the drugs of choice for chemotherapy of the intestinal tract. Coliform bacilli (*Escherichia coli* and *Aerobacter aerogenes*) are gram-negative organisms that occur along with the enterococci (*Streptococcus fecalis*), staphylococci, clostridia, yeasts, and aciduric bacteria in the intestinal tract. These normal intestinal flora may be augmented by other species such as *Proteus* and *Pseudomonas aeruginosa.* There is evidence that in addition to recognized intestinal pathogens some of these "normal" bacteria may be of etiologic significance in gastrointestinal infections and disease.

In the intestines these sulfonamides are hydrolyzed to sulfathiazole, especially in the lower bowel, where sulfathiazole is poorly absorbed, and a high concentration is attained. Although not bacteriostatic at low levels, sulfathiazole will inhibit coliform and other intestinal bacteria in these high concentrations. As a result of continued administration over a period of several days, these drugs will so reduce and alter bacterial flora that the feces become small in bulk.

Succinylsulfathiazole is administered orally in doses of 0.25 gm./kg. of body weight every 4 hours for 7 to 14 days. Phthalylsulfathiazole is given in doses of 0.125 gm./kg. of body weight initially, or divided into equal parts and administered every 6 to 8 hours. Dosage is continued daily over a period of several weeks.

Succinylsulfathiazole, phthalylsulfathiazole, phthalylsulfacetamide, and salicylazosulfapyridine have been used in the treatment of intestinal inflammation of bacterial origin. These drugs are employed in the presurgical treatment of patients undergoing elective surgery of the intestines. The reduction in intestinal contents, the gelatinous character of the fecal mass, and the reduced danger of peritonitis from fecal contamination are advantages which accrue from the use of the sulfonamides.

Phthalylsulfacetamide has also been used in the treatment of bacterial enteric infections. Phthalylsulfathiazole decreases the bowel contents and thus minimizes trauma of ulcerated lesions of the intestinal tract associated with *amebiasis*, *giardiasis*, and *paratyphoid* infections. Sulfadiazine is preferred by some clinicians for these infections.

The relatively insoluble sulfonamides and sulfadiazine have also been employed in the treatment of acute bacillary dysentery and in the elimination of the infection in mild dysentery carriers. Sulfonamide drugs are relatively inexpensive, and for this reason economy dictates their use in the large areas of the world where dysentery is a common medical problem.

From 1 to 7 per cent of the dose of these sulfonamides is absorbed, and in sensitive persons skin reactions with erythema nodosum may follow their administration.

**Sulfonamides applied locally.** It is clear that the use of crystalline sulfonamides as topical agents is not useful in the management of wound infections or the treatment of skin or mucous membrane infections. Topical application in burns and superficial infections is to be discouraged. Cutaneous sensitization is an imminent hazard in the use of sulfonamide drugs in any form. Toxic quantities of the drug can be absorbed from large denuded surfaces of the body.

The unusual properties of sulfamylon (Marfanil) have been referred to. This sulfonamide is about 10 times as soluble in water as sulfanilamide. Further, it is effective against organisms made resistant to other sulfonamides and is not antagonized by PABA. These properties have suggested its use in topical applications.

Sulfamylon has been used in external otitis and chronic otitis media by instillation of a 1 per cent solution 3 times a day.

The sodium salt of sulfacetamide (Sulamyd) has been used as a locally-applied sulfonamide by numerous workers. *Sulfacetamide Sodium Ophthalmic Ointment, U.S.P.*, is a 10 per cent ointment and *Sulfacetamide Sodium Ophthalmic Solution, U.S.P.*, is a 30 per cent buffered solution. Used in acute and chronic infections of the eye, the compound apparently penetrates ocular tissue rapidly and appears within the substance of the cornea in 15 minutes. It is not locally irritating. *Sulfisoxazole Diethanolamine Ophthalmic Ointment, U.S.P.*, 4 per cent, and *Sulfisoxazole Diethanolamine Ophthalmic Solution, U.S.P.*, 4 per cent, are similar dosage forms.

In general, the topical use of sulfonamides is contraindicated. Ophthalmic applications may be justified in some cases.

**Summary of therapeutic use of sulfonamides.** An attempt has been made in this chapter to present the advantages and disadvantages of sulfonamide chemotherapy. The physician now has better criteria in selecting sulfonamide or antibiotic therapy. The newer and less toxic sulfonamides are free from the criticism of crystalluria. The antibiotics have become less expensive and there is a wide choice of orally active dosage forms. It would appear that for infections caused by susceptible strains of organisms a dosage schedule as outlined previously, employing the mixture of sulfadiazine, sulfamerazine, and sulfamethazine is satisfactory. Clinical experience indicates that the more soluble and less acetylated single sulfonamides such as sulfisoxazole (Gantrisin) and sulfadimetine (Elkosin) may be the drugs of choice. These drugs give comparable results if administered properly. The low-dose, long-acting sulfonamides sulfamethoxypyridazine (Midicel, Kynex) or sulfadimethoxine (Madribon) have the decided advantage of lower total dose, more feasible dosage schedules, and anti-bacterial actions comparable to other sulfonamide drugs. Sulfamethoxazole (Gantanol) within a relatively brief period has proved to be a satisfactory drug in the treatment of many gram-positive and gram-negative infections of the genitourinary tract. As is pointed out in the section on antibiotic therapy, there are special cases where combined sulfonamide and antibiotic medication is indicated.

In a double blind study with sulfadimethoxine and tetracycline in the treatment of acute upper respiratory infections, Katsampes and McNabb (1960) found the sulfonamide preferable. Both drugs were equally effective as anti-bacterial agents and were equally nontoxic, but the authors believed that a superimposed staphylococcal infection would be avoided by the selection of the sulfonamide. A discussion of the choice of the most suitable anti-bacterial agent is given at the end of Chapter 10.

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# 10

# *The Antibiotics*

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## The Antibiotic Agents

Almost all microorganisms inhabiting a natural environment are subject to antagonistic as well as favorable reactions to the presence of other types of living organisms. Bacteriologists have recognized for many years that a growing culture of one microorganism may be inhibitory to the growth of another microorganism. As early as 1877, Pasteur and Joubert observed that certain air-borne bacteria were capable of inhibiting the growth of anthrax bacilli.

*Symbiosis* is the association of microorganisms that exert a mutual favorable influence on each other. If the association is unfavorable, an *antibiosis* exists. Any substance elaborated by a growing microorganism under such conditions may be spoken of as an *antibiotic.*

In modern terminology the word "antibiotic" has been employed to designate *a chemical substance, produced by or derived from living cells, which has a lethal or inhibitory action on microorganisms, especially a substance produced by living bacteria, actinomycetes, yeasts, molds, and other plants.*

A number of antibiotics have become important therapeutic agents. The properties of these substances and their field of usefulness will be discussed in this chapter. Their special clinical use in tuberculosis will be considered in the following chapter. Recently, emphasis has been placed upon the discovery of antiprotozoan and antifungal antibiotics, as well as anti-bacterial agents. Several such antibiotics have been found to be clinically effective in protozoan and fungal infections. In addition, some antibiotics are carcinostatic and will inhibit experimental carcinomas in animals. Thus this class of drugs has opened a new approach to the control of many diseases. Indeed, some idea of the significance of antibiotics in modern drug therapy is conveyed by the fact that over 6.3 million pounds were produced in the United States in 1962.

In this chapter the major antibiotics are considered in terms of their historical discovery and the subsequent isolation or synthesis of related drugs. Systematic studies have been made to determine the distribution of antibiotic substances in nature. Antibiotics have been found to be present in many natural forms of animal and plant life; their isolation, however, is difficult. According to Burkholder (1959), mycophenolic acid was the first mold antibiotic. It was prepared in crystalline form in 1896. No purified product of therapeutic value was isolated until 1939, when Dubos succeeded in preparing in crystalline form an antibiotic from *Bacillus brevis.* Today, through the use of genetic technics, artificial mutation, and selective biosynthesis, it is possible to control the kind and quantity of an antibiotic that some species of streptomyces and varieties of the penicillium mold produce.

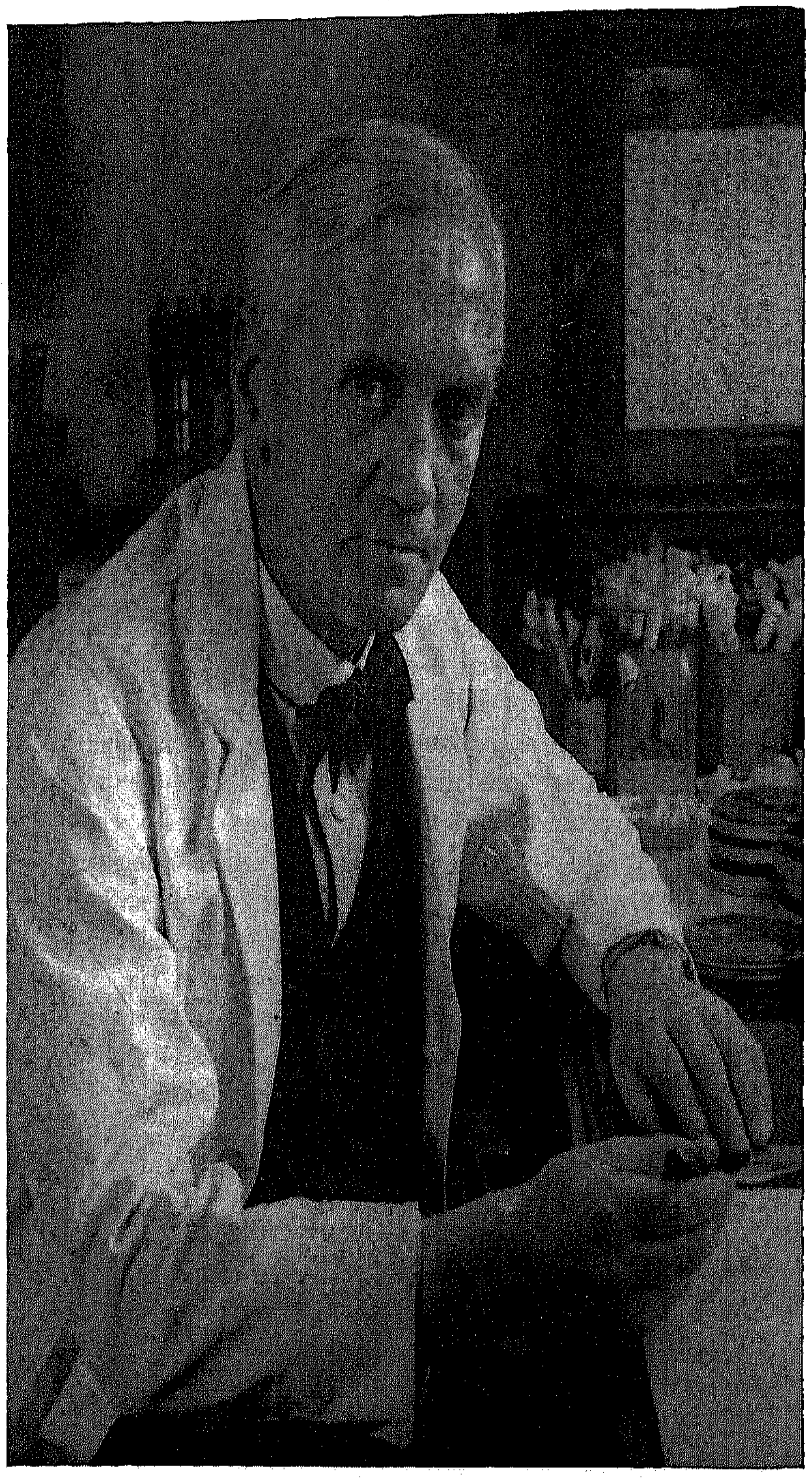
Within the past 25 years a world-wide search has been made for antibiotic-producing organisms in nature. A large number has been found. Only a few of these antibiotics are useful in treating the diseases of man, but applications are being found for many antibiotics in the control of plant and animal diseases. Antibiotics are used extensively as animal feed supplements and in the preservation of poultry and freshly caught seafood.

A systematic search for antitumor antibiotics has been conducted by the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, and the pharmaceutical industry. Antitumor antibiotics have been discovered which have a potential use in the control of malignant disease. Azaserine, actinomycin, mitomycin-C, actinobolin, streptovitacin A, 6-diazo-5-oxo-L-norleucine (DON), psicofuranine, streptonigrin, and refuin have been described as active against experimentally induced tumors in animals. Many of these antibiotics have been given clinical trials in man. Unfortunately, the toxic effects of bone marrow changes and kidney or liver damage have precluded extensive therapeutic applications of these agents. Refuin, from the Hebrew word for medicinal, may have a selective tumor cell-inhibiting action without affecting normal cells. The extensive literature on this subject cannot be reviewed here. The possibility exists, however, that nontoxic, antitumor antibiotics may be discovered.

The antibiotics have become useful tools for the study of biochemical cellular mechanisms. The discovery in 1960 of the ability of the actinomycins to complex with DNA made available an entirely new method of investigating DNA-dependent syntheses in bacteria, tumor cells, and the DNA viruses. Actinomycin inhibits DNA synthesis and has little influence on RNA or on the protein synthesis of bacteria. These actions have been extended to the multiplication of a DNA virus. It has been observed that in tissue culture actinomycin-D inhibits the multiplication of a DNA virus but not a ribonucleic acid virus. Thus it is possible to uncouple RNA synthesis from both DNA and protein synthesis by the antibiotic until RNA synthesis in the host cells is completely suppressed. In this way, the antibiotic provides a means for studying messenger RNA and virus multiplication. This very active field of investigation has been reviewed by Gale (1963) in a report on mechanisms of antibiotic actions.

## The Penicillins

**Discovery.** In 1928 Alexander Fleming, at St. Mary's Hospital, London, observed a contamina-



SIR ALEXANDER FLEMING
1881–1955
*The Discoverer of Penicillin*
"The contamination in 1928 of a culture plate by spores of a species of *Penicillium* was the beginning of the study of penicillin."

tion of a culture plate of staphylococci by spores of a species of *Penicillium* mold. Such contamination is not uncommon in bacteriologic work and must have been observed many times previously. In this particular instance the culture plate contained staphylococcal colonies which had been well developed and now were showing signs of dissolution. This extraordinary and unexpected finding prompted further investigation.

Fleming noted that the bacterial colonies surrounding a large colony of the contaminating mold had become transparent and obviously were undergoing lysis. Because of this observation, he suspected that the mold elaborated a material antagonistic to the growth and development of the staphylococcus organisms (fig. 10-1). Subsequent experiments proved this observation to be correct. Fleming demonstrated that the contaminating mold could be grown in a special medium and that the culture broth contained a potent anti-bacterial substance. The material was shown to be effective against a variety of gram-positive organisms and to be nontoxic to animals. Fleming gave the name *penicillin* to this antibiotic substance. This nomenclature was adopted by Fleming because of the established custom of naming an active principle after the parent substance with the ending "in": for example, *digitalin* from *digitalis* and *aloin* from *aloes*.

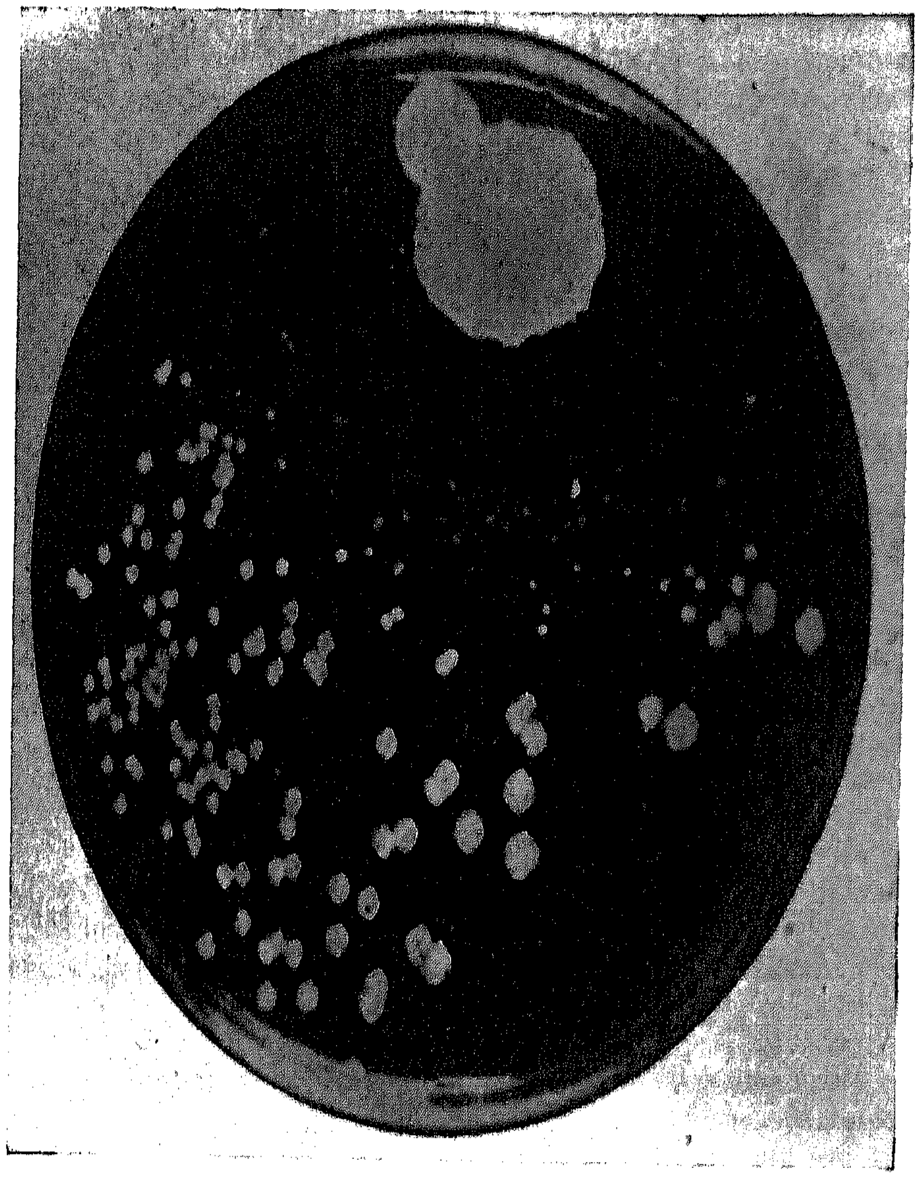


FIG. 10-1. Photographic print of the original culture plate on which the action of penicillin was observed.

The large colony of mold growth to the left has inhibited the growth of the staphylococcal colonies adjacent to it.

*(Fleming: Penicillin, Its Practical Application. Butterworth and Company, Ltd., 1946.)*

Fleming described the results of his experiments in 1929 and suggested the use of this agent in suppressing the growth of contaminating organisms in the selective culture of *Bacillus influenzae* from sputum. He also suggested that the filtrate of this penicillium culture might be used as "an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes." The strength of the broth culture of penicillin was such that it could be diluted nearly 1000 times before it lost its bacteriostatic power against staphylococci. In marked contrast to previously known anti-bacterial substances that were toxic to animal tissue in nearly all effective concentrations, penicillin was without toxicity to human leukocytes.

Raistrick, in further exploring Fleming's discovery, was successful in growing penicillium mold on Czapek-Dox medium, a synthetic medium containing glucose and salts. He and his colleagues at the London School of Hygiene demonstrated that penicillin was an organic acid that could be extracted from the acidified culture fluid by ether and that the compound was thermolabile. In 1932 they published their results, and because of difficulties in obtaining bacteriologic assays and clinical testing of their products, they discontinued the study.

In 1930 Raistrick sent to Thom in the United States a culture of a strain of the mold he had received from Fleming which was suspected of having been misnamed. This strain of *P. notatum* was distributed to interested investigators by Thom and Raper in 1930 and succeeding years. Reid in 1935 studied the nature of the inhibitory substance produced by this mold when grown on a veal infusion broth or on a modified Czapek-Dox synthetic medium as described earlier by Clutterbuck, Lovell, and Raistrick. He found that the "antibiotic" produced was selective in its antibacterial action and confirmed these workers' observation that the pigment produced by the mold was not bactericidal. Reid studied the effect of heat, light, oxygen, hydrogen, and carbon dioxide upon the production of the active material and found the substance to be extremely unstable.

Despite these observations, no clinical interest in penicillin developed until Chain and Florey, at Oxford, confirmed Fleming's findings and isolated an impure penicillin in the form of a brown powder in 1940. The Oxford workers showed further that aqueous solutions of the drug could be administered to animals in large doses with little evidence of toxic effects. Penicillin afforded almost complete protection against *staphylococci*, *streptococci*, and *Clostridium septique* infections in mice. Untreated control animals died within 17 hours, while all treated mice, with the exception of those receiving the smallest doses, survived. These experiments showed that penicillin was the most powerful chemotherapeutic agent known against these infections. In 1941 these same workers published, with Abraham, the results of their experiments. They described the preparation and properties of penicillin and the favorable clinical results which they had obtained in a number of cases of fulminating pyogenic infections.

In 1941 an aroused scientific interest in the therapeutic possibilities of this new drug resulted in arrangements for the production of penicillin in the United States. In order to facilitate and coordinate investigations with penicillin, the Committee on Medical Research of the National Research Council arranged to supervise the distribution of penicillin for clinical research. Widescale clinical investigation was conducted, and the results were collected, collated, and summarized by this Committee. These showed the remarkable therapeutic efficacy of the antibiotic.

**Production.** Many kinds of penicillins are produced by various strains of *P. notatum* and *P. chrysogenum*, as well as by some other molds. A high-potency strain of fungi must be selected for good yields of penicillin G. Strains of the mold from different sources vary widely in their yield of the drug. In 1943 a systematic search was undertaken by the U. S. Department of Agriculture Northern Regional Research Laboratory at Peoria, Illinois, to isolate from nature as many representatives of the *Penicillium notatum-chrysogenum* group as possible, and to test for their capacity to produce penicillin. Strains were isolated from food products, fruits and vegetables, and from soils collected by the Army Air Transport Command in the United States and in many foreign countries. No strain was discovered that, for surface culture methods, exceeded in penicillin-producing capacity a substrain of the original Fleming mold. However, for submerged culture methods, a strain was isolated, ironically enough, from a cantaloupe collected in Peoria that has served for the development of a series of superior penicillin-producing substrains. By exposing cultures of *P. chrysogenum* to x-ray and ultraviolet radiation, and then beginning new colonies from individual spores, new strains have been produced. Seven penicillins, designated as G, K, X, O, V, F, and dihydro F, have been isolated from natural media.

Penicillin production in the United States has reached enormous proportions. In the year 1961 over one million pounds of penicillin were produced. This antibiotic is used in animal feed supplements in considerable quantity, but the greatest amount is used in human and veterinary medicine.

## Chemistry of the penicillins.

**Biosynthetic penicillins.** Attempts to increase the penicillin yield of the mold culture by the addition of chemical intermediates have led to the discovery of new penicillins; several have been obtained in yields representing as much as 60 to 100 per cent of the total penicillin formed. By this method, 34 new crystalline biosynthetic penicillins were isolated. It was further discovered that by feeding the mold a precursor of phenylacetic acid or the acid itself, the amount of benzyl penicillin G formed could be substantially increased. Phenoxymethyl penicillin V was made by this method, employing N-(2-hydroxyethyl)-phenoxyacetamide as a precursor, with strains of *P. notatum*.

These findings have considerable practical significance. The amount of benzyl penicillin G produced by the mold in commercial production can be encouraged and the proportion of heptylpenicillin K decreased. Experimental and clinical experience has demonstrated that K is less effective than G in the treatment of infections. This technic also made feasible the commerical production of crystalline penicillin, since crystallization requires that a predominant quantity of a single penicillin be present.

The general structure of the penicillins is shown in table 10-1. The thiazolidine ring nucleus (A) is fused to a $\beta$-lactam ring (B) which is attached to a side chain $(R{-}\overset{|}{C}{=}O)$. Any chemical modification of the $\beta$-lactam or thiazolidine rings destroys the anti-bacterial activity of the molecule, *e.g.*, penicillinase breaks the $\beta$-lactam ring.

Many salts of the penicillins have been made as shown in table 10-1. These salts determine the solubility of the antibiotic. The very soluble sodium salt is available for intravenous use; the benzathine salt, very slowly soluble, is absorbed gradually from an intramuscular injection depot over a 2- to 4-week period.

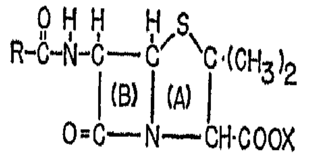
Modification of the prosthetic group R, attached to the 6-aminopenicillanic acid portion of the molecule, determines the relative stability of the form of penicillin to penicillinase. The more complex prosthetic groups impart a greater degree of stability to hydrolysis by penicillinase.

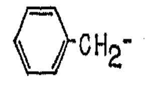
Benzyl penicillin G was synthesized by condensing two major constituents of the molecule that had previously been identified as decomposition products of natural penicillin. Penicillin V, phenoxymethyl penicillin, was synthesized by Sheehan and his associates in 1957 by cyclization of penicilloic acid. By 1950, several hundred different penicillins had been obtained by adding various side-chain precursors to fermentations of *P. chrysogenum*. It was only after the total chemical synthesis by Sheehan of phenoxymethyl penicillin, a compound prepared 10 years before by biosynthetic methods and discarded, that the acid stability of this form of penicillin was recognized. This property is believed to make it particularly useful for oral administration. That this belief is not necessarily true is pointed out in the section on oral administration of the penicillins.

In 1959 Sheehan and his associates succeeded in the synthesis of 6-aminopenicillanic acid by a novel organic chemical route. The existence of this basic nucleus had been suspected for some time as a fermentation product of *P. chrysogenum*. In 1959 the acid was first made available in quantity by the discovery of Batchelor *et al.* (1959) that it could be crystallized from fermentations to which no side-chain precursor had been added. 6-Aminopenicillanic acid has a very low anti-bacterial activity, but it can be acylated readily to yield different penicillins that are powerful antibiotic drugs. The availability of this key intermediate made possible the large scale production of semi-synthetic penicillins. Several thousand new penicillins have been obtained in this way (Abraham and Newton, 1961).

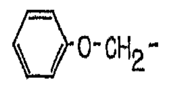
TABLE 10-1

*Types of Penicillins*

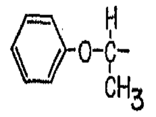




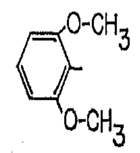
Benzyl penicillin (G)



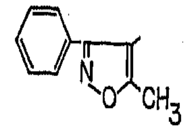
Phenoxymethyl penicillin (V)



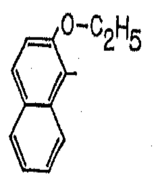
Phenoxyethyl penicillin (phenethicillin)



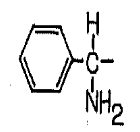
2,6-Dimethoxyphenyl penicillin (methicillin)



5-Methyl-3-phenyl-4-isoxazolyl penicillin (oxacillin)



6-(2-Ethoxy-1-naphthamido) penicillin (nafcillin)



6α-Aminobenzyl penicillin (ampicillin)

X, Sodium, potassium, aluminum, procaine, benzathine salts, or free acid.

## Types of penicillins and dosage forms.

**Sparingly-soluble salts of penicillin.** Repository penicillins are made by preparing a sparingly-soluble salt. Procaine penicillin G is such a dosage form. Crystalline procaine penicillin is administered suspended in peanut oil, sesame oil, or in aqueous suspension. Similar preparations of procaine penicillin G in oil to which 2 per cent aluminum monostearate has been added have a prolonged action. The usual dose is 300,000 units in 1 ml. once a day. These salts are recognized in the U. S. Pharmacopeia as *Procaine Penicillin G*, *Sterile Procaine Penicillin G Suspension*, and *Sterile Procaine Penicillin G with Aluminum Stearate Suspension*. These preparations are intended for intramuscular administration, and provide adequate blood levels for 12 to 24 hours after injection of suitable doses.

**Benzathine Penicillin G, U.S.P. (Bicillin, Neolin).** Dibenzylethylenediamine dipenicillin G in aqueous suspension is a long-acting penicillin dosage form. This preparation is supplied for intramuscular injection in vials containing 600,000 units of the penicillin salt in each ml. One intramuscular injection will supply a detectable blood concentration for 1 to 4 weeks, depending on the size of the dose.

**Phenoxymethyl Penicillin, U.S.P. (V-Cillin, Pen-Vee).** Phenoxymethyl penicillin demonstrates an anti-bacterial activity equivalent to the soluble salts of penicillin G. Because gastric acidity does not markedly affect its potency, it may be administered orally without regard to mealtimes. It is well absorbed from the gastrointestinal tract, and high blood levels are obtained readily.

**Potassium Phenoxymethyl Penicillin, U.S.P. (V-Cillin K, Compocillin-VK, Pen-Vee K).** The advantage of the potassium salt of penicillin V appears to be its immediate solubility in the duodenum and its rapid absorption from the upper portion of the small intestine. The blood levels reached within the first 2 hours after oral administration are at least 4 times those from comparable doses of penicillin G. Peak levels of the order of magnitude of 6 and 8 units per ml. are achieved after the administration of 250 mg. of potassium phenoxymethyl penicillin. The disappearance from the blood of potassium phenoxymethyl penicillin is not more rapid than that of phenoxymethyl penicillin V free acid.

Potassium phenoxymethyl penicillin is available in 125-mg. (200,000 units) and 250-mg. (400,000 units) tablets.

**Hydrabamine Phenoxymethyl Penicillin V (Compocillin).** This preparation is a mixture of penicillin V salts consisting chiefly of the salt of N,N′-bis(dehydroabietyl) ethylenediamine, with small amounts of the salts of dihydro and tetrahydro derivatives. It is a water-insoluble di-penicillin compound salt of a rosin amine base. It has about the same toxicity in animals as benzathine penicillin G. It is administered orally for acute infections in initial doses of 300,000 to 600,000 units every 6 hours. Subsequent doses are regulated according to the therapeutic response.

**Potassium Phenethicillin (Alpen, Chemipen, Darcil, Dramcillin-S, Maxipen, Semopen, Syncillin).** This antibiotic is α-phenoxyethyl penicillin. Chemically, phenethicillin is closely related to penicillin V, but it contains an additional $CH_3$ group which renders the adjacent carbon atom asymmetric. The synthetic form occurs as a mixture of two isomers.

Phenethicillin exhibits many desirable properties as an antibiotic. It is quite stable in gastric acid, it is efficiently absorbed from the gastrointestinal tract, the blood levels are quickly attained, and peak values are twice as high as equivalent oral doses of penicillin G or V. The anti-bacterial spectrum and clinical use of phenethicillin is similar to other penicillins. Potassium phenethicillin is available in 125- and 250-mg. tablets for oral use.

**Sodium Penicillin O (Cer-O-Cillin).** Penicillin O is allylmercaptomethyl penicillin. It has the same anti-bacterial spectrum as the soluble forms of penicillin G. It is said to be less toxic to experimental animals and to give rise to a lower incidence of allergic reactions in man than other varieties of penicillin. Untoward reactions have occurred following its use. Penicillin O is combined with chlorprocaine to yield a water-insoluble salt. Its use is similar to procaine penicillin G. The preparation is known as *Depo-Cer-O-cillin chlorprocaine*.

**Sodium Methicillin (Dimocillin, Staphcillin).** Sodium methicillin is a semi-synthetic penicillin administered by parenteral injection. It is highly resistant to inactivation by penicillinase, and its anti-bacterial spectrum is comparable to that of other penicillins. It is effective against some forms of penicillin G-resistant staphylococci. It is available as a sterile powder in 1-gm. vials for the preparation of the intravenously or intramuscularly injected solution. The adult dose is 1 gm. in 1.5 ml. of water or saline every 4 to 6 hours. Sodium methicillin is very unstable in solution at an acid pH. For this reason, it is completely ineffective when administered orally. Its solutions should be freshly prepared.

**Sodium Oxacillin (Prostaphlin, Resistopen).** Sodium oxacillin is a semi-synthetic penicillin intended for oral use. It is effective against penicillin G-resistant staphylococci and is highly resistant to inactivation by penicillinase. It is well absorbed when given orally between meals. It is available in 250-mg. capsules as the sodium salt. The usual adult dose for mild staphylococcal infections is 500 mg. every 4 to 6 hours for at least 5 days. In severe infections the dose is 1 gm. every 4 to 6 hours. This form of penicillin is more stable in acids than penicillin G but not as stable as phenozymethyl penicillin or potassium phenethicillin.

**Sodium Nafcillin (Unipen).** Sodium nafcillin is a soluble penicillin with bactericidal activity *in vitro* against strains of *S. aureus* resistant to penicillin G. It has the usual penicillin activity against pneumococci and streptococci. It is used orally or parenterally. In severe infections the dose is 0.5 to 1.0 gm. every 4 hours, dissolved in 15 to 30 ml. of sterile normal saline or distilled water and either injected intravenously over a 5-minute period or given by slow intravenous drip. The intramuscular dose is 0.5 gm. every 4 to 6 hours. The adult oral dose for mild infections is 250 to 500 mg. every 4 to 6 hours. In severe infections 1 gm. every 4 to 6 hours may be necessary. It is preferred that the oral dose be taken 1 to 2 hours before meals. The microbiologic and therapeutic effects of sodium nafcillin appear to be similar to those of oxacillin and methicillin. Nafcillin is resistant to inactivation by staphylococcal penicillinase. It is recommended primarily for the therapy of severe infections caused by penicillin G-resistant staphylococci.

**Ampicillin (Polycillin).** Ampicillin, unlike the other varieties of penicillin, is active against a number of gram-negative microorganisms. Its anti-bacterial spectrum against gram-positive pathogens resembles the other penicillins. Penicillinase-producing staphylococci are resistant to ampicillin.

Ampicillin is stable in an acid medium, and the drug is very well absorbed after oral administration, although the rate of absorption is somewhat slower than that of other forms of penicillin. Increasing the dose will increase the concentration of the antibiotic in the blood. Levels in the blood which exceed the concentrations obtained with most broad-spectrum antibiotics have been reported. In general, the blood level is proportional to the dose. Ampicillin is excreted in the urine in high concentrations; about 25 to 30 per cent of a dose can be recovered in the urine (Bunn, 1961).

Ampicillin is not markedly bound to plasma protein and thus is believed to provide a comparatively greater amount of the antibiotic in an active form in the blood for a given dose.

The chief value of ampicillin is its effectiveness against infections caused by gram-negative bacteria, especially tetracycline-resistant coliform bacteria or strains of *Proteus*, diarrheal diseases caused by salmonellae, typhoid fever, shigellae, and meningitis caused by *H. influenzae*. According to Rolinson and Stevens (1961), ampicillin is about 10 times more active against gram-negative bacilli generally than penicillin G, and only slightly less active against gram-positive cocci. They compared this form of penicillin to tetracycline and chloramphenicol for its activity against gram-negative organisms, and termed it a "broad-spectrum penicillin."

Ampicillin appears to be well tolerated, although gastrointestinal disturbances and allergic reactions have been produced by the antibiotic. Skin rash and pruritus are the most common side effects. The usual precautions observed with any of the penicillins should be taken with ampicillin.

The adult dose is 250 to 500 mg. orally every 6 hours, according to the nature of the infection. It has been reported useful in the treatment of respiratory, genitourinary, and gastrointestinal tract infections. The relative clinical effectiveness of ampicillin as compared to other forms of penicillin has not been determined.

The discovery of this variety of penicillins significantly enhances the scope of penicillin chemotherapy. The physician has available penicillinase-resistant, acid-stable, and now gram-negative anti-microbial activity in different varieties of penicillins.

## Unit.

The *International Standard Unit* and the *U.S.P. Unit* for penicillin is that activity which is present in 0.6 microgram of the standard crystalline sodium salt of penicillin G. One milligram of crystalline standard penicillin will thus contain 1667 International or U.S.P. Units. One gram of crystalline penicillin G sodium is equivalent to approximately 1.5 million units. Thus a 300,000-unit dose is approximately 0.2 gm. of the salt.

Fortunately, the doses of the newer salts and varieties of penicillin are expressed as mg. and not as units. The U.S.P. XVI gives the following weight-unit relationships (expressed in U.S.P. Units per milligram):

| | |
|---|---|
| Phenoxymethyl penicillin V | 1695 |
| Potassium phenoxymethyl penicillin V | 1530 |
| Benzathine penicillin G | 1211 |
| Potassium penicillin G | 1595 |
| Procaine penicillin G | 1009 |
| Sodium penicillin G | 1667 |

## Assay.

Penicillins inhibit the growth *in vitro* of staphylococcus, streptococcus, and *B. subtilis* in a manner suitable for quantitative measurement. By comparison of growth inhibition produced by a suitable dilution of a standard penicillin G with an unknown, an estimation of its potency may be made. The degree of growth inhibition is evaluated by measurement of the size of the clear zone on an agar plate surrounding the cup containing the penicillin solution. The cup-plate assay method is used most extensively in determining the penicillin concentration in biologic fluids, *e.g.*, blood and urine. This bacteriologic method may be employed to determine the susceptibility of an infecting strain of pathogenic organism to a variety of penicillins, and thus to estimate the effectiveness of this drug in anti-bacterial therapy. Indeed, if time permits, the bactericidal activity of the antibiotic should be demonstrated in the laboratory before the drug is used therapeutically.

### Penicillinase.

Abraham and Chain in 1940 discovered that certain penicillin-insensitive organisms produced a substance of enzyme character which destroyed penicillin. They named this substance "penicillinase." There are probably as many different penicillinases as there are strains of bacteria producing them. These are found chiefly in the *Bacillus subtilis-mesentericus* group.

The enzyme is usually obtained from culture filtrates of a strain of *B. cereus*. It has the specific property of inactivating penicillin by splitting the bond linking the nitrogen of the thiazolidine ring to the adjacent carbonyl carbon atom, thus releasing an inactive penicilloic acid. It is most active at body temperature at a pH of 6.5. Active penicillinase preparations are employed to neutralize the anti-bacterial power of penicillin in blood or other body fluids and to permit the development of bacteria in cultures which otherwise would be inhibited by the penicillin. In mixed infections penicillinase-producing organisms may be present in sufficient numbers to protect penicillin-sensitive organisms from the action of the drug. Penicillinase can be utilized for the purpose of testing the sterility of penicillin dosage forms. In practice, a sterile solution of hydroxylamine hydrochloride is often preferred for this purpose. The use of this chemical avoids the employment of the enzyme, which is of variable potency and composition.

An organism's ability to produce penicillinase apparently is not entirely related to its resistance to penicillin. Many initially resistant organisms do not produce penicillinase. In addition, the acquisition of resistance by strains of organisms derived from initially sensitive species is not necessarily accompanied by the production of penicillinase. Further, some penicillin-sensitive organisms have been reported to be capable of elaborating penicillinase. It would appear that the explanation for the sensitivity or resistance of different organisms to penicillin must be sought in the area of biochemical differences.

Until recently, staphylococcal penicillinase had not been studied. It is now known that the enzyme produced by some strains of *Staphylococcus aureus* is partly extracellular and partly intracellular. In addition, exposure of these microorganisms to penicillin G and other varieties of penicillins, including methicillin, induces penicillinase production. One must distinguish between the relative *initial* resistance to bacterial penicillinase by a form of penicillin and the emergence of resistant strains of staphylococci by repeated or prolonged exposure to the antibiotic.

Penicillinase preparations have been used to treat penicillin allergic reactions; however, epinephrine is preferred.

### Pharmacology.

Pharmacologically, penicillin is relatively inert. For most patients, its relative harmlessness, contrasted with its potent anti-bacterial action, makes its therapeutic use one of extraordinary simplicity.

Intravenous doses of penicillin G and other varieties of penicillin in excess of those used in therapy have little effect on cardiac activity or respiration. The antibiotic is essentially inactive on red blood cells, the perfused frog heart, or isolated smooth muscle preparations in the laboratory. Large, repeated, daily intravenous doses of penicillin to mice are without significant pharmacologic effects. Of all animal species, the guinea pig appears to be especially sensitive. Daily doses of 7000 units per kg. produce serious toxic symptoms, and at necropsy, necrotic and hemorrhagic lesions are found in the liver, kidneys, adrenals, and heart muscle. It has been estimated that penicillin is between 100 and 1000 times more toxic to guinea pigs than to mice and rabbits.

The intravenous LD$_{50}$ of pure penicillin G in mice is 3,500,000 units per kg. of body weight. Anesthetized cats given single intravenous doses of 500,000 units per kg. of pure penicillin G sodium have been reported to exhibit a moderate fall of carotid blood pressure and a slight stimulation of respiration.

Penicillin is without effect on leukocytes. In anti-bacterial amounts penicillin does not interfere with the migration or growth of tissue elements such as lymphocytes, fibroblasts, or macrophages.

Amorphous and crystalline penicillin may have a slight retarding effect upon the clotting time of normal human blood. Crystalline penicillin G sodium solutions do not interfere with the oxygen consumption of yeast cells, duck erythrocytes, or slices of rat liver.

All of the commercially available varieties of penicillin are equivalent to penicillin G pharmacologically and toxicologically. All forms of penicillins have the ability to produce serious toxic sensitization reactions.

It is now well recognized that in contact with brain tissue penicillin has a pronounced toxic effect. Penicillin in the central nervous system produces stimulation, twitching, and convulsions. Penicillin applied to the cortex of rabbits or injected into the cortex produces *edema*, *ischemic degeneration*, *hemorrhage*, and *massive necrosis*. Penicillin cannot with safety be applied to brain tissue locally in concentrated solution. It is generally agreed that untoward reactions are more likely to occur with concentrated solutions (5,000 to 50,000 units per ml.) than with dilute solutions (1,000 units per ml.). To avoid such complications, in meningitis therapy dilute solutions of penicillin are used.

The convulsive syndrome resulting from local application of penicillin to the central nervous system is readily controlled by the use of the soluble barbiturates intravenously.

### Absorption and distribution in the body.

Penicillin G is rapidly absorbed from the gastrointestinal tract. A considerable portion is lost by oral administration, however, as a result of inactivation by the acidity of the stomach or by penicillinase-producing bacteria in the lower intestinal tract. For these reasons it is generally agreed that to obtain satisfactory blood levels by oral dosage it is necessary to administer from 3 to 6 times the usual parenteral dose. Other varieties of penicillin can be administered orally for therapeutic purposes, with the exception of methicillin, which is destroyed by the acidity of the stomach.

So many varieties and dosage forms of the penicillins are available that the physician must be familiar with the specific drug preparation he is using.

The various forms of penicillin are absorbed at different rates from the gastrointestinal tract or from injection sites. These factors are considered in the descriptions of the different salts and dosage forms of penicillin. Following administration, penicillin is distributed throughout the body. Most tissues are permeable to penicillin after it reaches the blood. This is an important factor in its therapeutic efficacy.

In general, the bone marrow, brain, cerebrospinal fluid, cornea, lens, and vitreous humor contain only small amounts of penicillin after the intravenous administration of large doses of the drug. Low concentrations are reached in joints and pericardial and pleural fluids. Only a small amount of penicillin is found in skeletal and cardiac muscle, while a much higher concentration is found in the *liver*, *bile*, *lungs*, *intestine*, *ascitic fluid*, and *skin*. Penicillin does not penetrate into pus or abscess fluid, but it does penetrate fibrin blood clots.

Penicillin is transmitted through the placenta. However, in the treatment of acute meningitis it does not permeate the blood-brain barrier following intravenous or intramuscular injection. In this condition penicillin may be administered by intraspinal injection, but it must be remembered that such penicillin injections are hazardous.

### Urinary excretion.

Renal excretion of the specific variety of penicillin plays a prominent role in determining the value of the antibiotic. In patients with normal kidney function, from 90 to 100 per cent of soluble penicillin G and its degradation products are excreted in the urine within a few hours after an intramuscular dose. Diminishing amounts are found in the urine for as long as 7 to 12 hours. The total penicillin-like substances in the urine may not be anti-bacterial, because a number of inactive metabolites are formed. In the presence of renal disease the drug is retained and the blood level remains high, although, unlike most drugs, toxic concentrations do not develop. *p*-Aminohippuric acid or probenecid, when used in conjunction with penicillin, compete with penicillin for tubular excretion, and the rate of penicillin excretion is reduced.

In general, most forms of penicillins are excreted rapidly in the urine; this is not the only element that controls the sojourn of the drug in the body. The factors of absorption, binding to serum protein, and tissue diffusion are more important in determining the anti-bacterial effects. Sodium methicillin and sodium ampicillin are excreted in the urine rapidly and unaltered, at a rate of from 35 to 50 per cent within 6 hours. Sodium oxacillin is excreted at a rate and to a degree that is approximately equal to penicillin G. Phenoxymethyl penicillin is excreted in the urine in higher concentrations than comparable doses of penicillin G. The significance of these values for the phenoxy penicillins has been discussed by Lee and Anderson (1962).

### Mechanism of action.

Extensive studies by numerous investigators have elucidated the mechanism of action of penicillin. It is now generally recognized that the most characteristic property of the anti-bacterial action of penicillin resides in *the inhibition of metabolic functions vital to the bacterial cell wall.*

Penicillin may be bactericidal or bacteriostatic, depending upon the age of the microorganism and the nature of the environment. Young, rapidly growing bacterial cells are most susceptible, whereas mature cells are neither lysed nor readily killed by penicillin. The bacteriolytic action is greatest during the period of the organism's maximal rate of multiplication.

An understanding of the mechanism of action of penicillin on bacteria was presaged by the work of Park and Johnson (1949). They found that three uridine nucleotides accumulated in staphylococci that had been treated for a brief time with penicillin. Subsequently the chief nucleotide was shown to consist of uridine pyrophosphate linked through the N-acetyl derivative of a novel amino sugar to a peptide containing D- and L-alanine, L-lysine, and D-glutamic acid. The amino sugar muramic acid is essential in the formation of the bacterial cell wall, according to current concepts. Analysis of the cell walls of gram-positive bacteria, which has been made possible by osmotic and centrifugation technics, has revealed that they contain only a relatively small number of different amino acids, and muramic acid. In addition, the proportion in which these elements occur in the cell walls of *S. aureus* is the same as in the nucleotide isolated in earlier studies (Gale, 1963).

These discoveries led to the hypothesis that the uridine nucleotide is an intermediate essential to the formation of new cell wall material. The muramic acid-peptide must pass through the nucleotide stage. However, in the presence of penicillin the nucleotide accumulates and cannot be utilized to form the bacterial cell wall. The concept is supported by the fact that penicillin inhibits C$^{14}$-labeled lysine from incorporation into the cell wall, and uridine nucleotides are known in other cases to mediate the linking of sugars and amino sugars to form complex compounds.

Park, Strominger, and their associates (1957 *et seq.*) have further elucidated the biochemical basis for the action of penicillin and its selective toxicity for bacterial cells. They suggest that the changes in morphology of bacteria induced by penicillin (swelling, filamentous forms, enlarged bodies) can be explained by the loss of the integrity of the cell wall that follows interruption of nucleotide cell wall synthesis. They hold the view that the selective toxicity of penicillin is related to its interference in a metabolic sequence that is not found in animal cells, the biosynthesis of the cell wall (Strominger, 1962).

The complete lack of toxicity of penicillin to animal cells is understandable if one accepts the concept that these cells do not synthesize structures that are chemically similar to the cell walls of bacteria. This is plausible, since muramic acid and D-amino acids have been found only in microorganisms. The significance of the major action of penicillin on young, growing bacteria is explained if the formation of new cell wall material is the only process affected. It is not until the cell begins to grow that the existing cell wall becomes inadequate.

**Spectrum of antibiotic activity.** In table 10-2 the microorganisms susceptible to penicillin are listed. In general, penicillin *in vitro* is active against gram-positive bacilli and certain gram-negative cocci. The gram-negative cocci can be classified into two groups on the basis of their penicillin susceptibility. Thus, *N. gonorrhoeae*, *N. intracellularis*, and *N. catarrhalis* are sensitive, while *N. flava* and certain other *Neisseriaceae* are not susceptible. Distinction must be made between the *in vitro* and the *in vivo* activity of penicillin. In addition, one must bear in mind that certain strains may or may not be susceptible, and that it is impossible to predict with certainty whether or not a given strain will be destroyed by the antibiotic. The discovery of ampicillin with bactericidal activity against a significant number of gram-negative pathogens requires a revision of the former classifications. This form of penicillin is active *in vitro* against gram-negative and gram-positive microorganisms, and it has been called a broad-spectrum penicillin (Rolinson and Stevens, 1961).

Eagle and Musselman (1948 *et seq.*) have demonstrated that the susceptibility *in vitro* of a given organism may be defined in terms of 3 penicillin concentrations. These are as follows:

1. The concentration that merely reduces the rate of multiplication. At this concentration the rate of bacterial division and growth is retarded. Not all organisms are killed.
2. The minimal effective concentration. This is

TABLE 10-2

*Recommended Major Antibiotics or Sulfonamides in Various Infectious Diseases*

| Disease | Microorganism | Drug Recommended* | | | | | |
|---|---|---|---|---|---|---|---|
| | | Penicillin | Streptomycin | Tetracyclines | Chloramphenicol | Sulfonamides | Erythromycin |
| Actinomycosis | *Actinomyces* | 1† | — | 1† | — | 2 | — |
| Amebiasis (intestinal form) | *E. histolytica* | — | — | 1 | — | — | — |
| Anthrax | *B. anthracis* | 1 | — | 2 | 2 | 3 | — |
| Bacillary dysentery | *Shigella* sp. | — | — | 1 | 1 | 1 | — |
| Brucellosis | *Brucella* sp. | — | 1† | 1† | 2 | 3 | — |
| Chancroid | *H. ducreyi* | — | 2 | 1 | 2 | 2 | — |
| Diphtheria‡ | *C. diphtheriae* | 1 | — | 3 | — | — | 2 |
| Friedlander's pneumonia | *K. pneumoniae*§ | — | 1† | 1† | 2 | 3 | — |
| Gonorrhea | *N. gonorrheae* | 1 | 3 | 2 | 3 | 2 | 3 |
| Granuloma inguinale | *D. granulomatis* | — | 1 | 2 | 3 | — | — |
| Lobar pneumonia | Pneumococcus | 1 | — | 3 | — | — | 2 |
| Lymphogranuloma inguinale | Virus | — | — | 1 | 2 | 3 | — |
| Meningitis¶ | *H. influenzae* | — | 3 | 1† | 2 | 1† | — |
| Plague‖ | *P. pestis* | — | 1 | 2 | 2 | 1 | — |
| Psittacosis | Virus | — | — | 1 | 1 | — | — |
| Staphylococcus infections# | *S. aureus* | 1 | — | 2† | 2† | — | 2† |
| Streptococcus infections§ | *S. pyogenes*, gr. A, B, C, G | 1 | — | — | — | — | 2 |
| | *S. viridans* | 1 | 1 | 3 | 3 | — | 2 |
| Syphilis | *T. pallidum* | 1 | — | 3 | — | — | 2 |
| Tuberculosis | *M. tuberculosis* | — | 1 | — | — | — | — |
| Tularemia | *P. tularensis* | — | 1 | 2 | 3 | — | — |
| Typhoid | *S. typhosa* | — | — | 3 | 1 | — | — |
| Typhus | Rickettsiae | — | — | 1 | 2 | — | — |
| Urinary tract infections | *A. aerogenes*** | — | 1† | 1† | 2 | 3 | — |
| | *E. coli*** | — | 2 | 2 | 2 | 1 | — |
| | *B. proteus*** | — | — | 2 | 1 | 3 | — |
| | *B. pyocyaneus*** | — | 1 | 3 | 3 | 3 | — |
| Vincent's angina | *Fusiformis fusospirochetes* | 1 | — | 3 | — | — | 2 |
| Yaws | *T. pertenue* | 1 | — | 2 | 2 | — | — |

* 1, first choice; 2, second choice, 3, third choice; —, not recommended or not effective.

† Combined therapy suggested.

‡ Useful in carrier state only to treat complications. Antitoxin indicated.

§ Bacterial sensitivity tests are usually necessary.

¶ Combined antibiotic and sulfadiazine therapy indicated.

‖ Combined streptomycin and sulfadiazine therapy indicated.

# Organism should be tested for sensitivity; acquired resistance probable (non-penicillinase producing organisms only).

** Organism must be tested for sensitivity.

the concentration which kills the organisms at a rate faster than they multiply. This results in a progressive decrease in the number of viable organisms. This value expresses the degree of susceptibility of the organism to penicillin. However, this is not the most effective therapeutic level.

3. The maximal effective concentration. This concentration kills the organisms at the maximal rate. This level differs from the minimal effective concentration, which will only *slowly* decrease the number of organisms. Concentrations higher than the maximal effective level *will not further increase the rate of killing in vitro.*

Many other factors are involved when this problem is transferred from the controlled, static conditions of the laboratory to the dynamic state of the body. They are stressed here because they apply to the use of all antibiotic agents.

### Therapeutic use.

A summary of the rôle of penicillin in modern anti-bacterial chemotherapy is given on page 123. Penicillin is chiefly effective against gram-positive organisms. Dramatic therapeutic results have been obtained with penicillin in the treatment of staphylococcal, streptococcal, pneumococcal, and clostridial infections. Gram-negative meningococcal and gonococcal infections also respond to penicillin therapy. In table 10-2 the infections susceptible to penicillin are tabulated.

Penicillin has a remarkable history in the treatment of syphilis. Prior to 1938 syphilis caused approximately 15,000 deaths annually in the United States. Following the discovery of penicillin, the incidence of primary and secondary syphilis had been reduced to one-tenth of the 1943 level by 1953, and an 82 per cent reduction in the mortality rate had been achieved by 1962. Venereal disease control programs were curtailed, and it was generally assumed that the remarkable effectiveness of penicillin would solve this public health problem. It is true that late symptomatic syphilis and congenital syphilis of the newborn have become relatively uncommon since the advent of penicillin therapy. However, the U. S. Public Health Service reported an alarming increase (174 per cent) in primary and secondary syphilis in the United States from 1957 to 1961. Marked increases in the disease were also observed in other countries. There is no evidence that *T. pallidum* has developed resistance to penicillin, and it is still generally believed that adequate case detection and antibiotic therapy will cure the disease.

A single treatment with 2,400,000 units of benzathine penicillin G can be used for the routine therapy of early and latent syphilis. If procaine penicillin G in oil and aluminum monostearate is used, routine therapy should consist of 4,800,000 units, with individual injections of 1,200,000 units every 2 to 7 days. This has been reported to give a cure rate of 94.6 per cent in secondary syphilis. Good results in the treatment of late symtomatic syphilis have been obtained with total doses of 6,000,000 to 10,000,000 units of procaine penicillin G in oil and aluminum monostearate. Individual doses of 1,200,000 units should be given 2 or 3 times a week.

For penicillin-sensitive persons, oral treatment with 50 mg. of erythromycin or carbomycin every 4 hours, 4 doses daily for 10 days, may be instituted. A total dose of 2 gm. is required.

Clinically, penicillin does not produce the response that would be expected in *diphtheria.* Levels can be established *in vivo* that are more than adequate for the control of the bacillus *in vitro.* Penicillin is not used in the treatment of clinical diphtheria. Penicillin is most useful as an adjunct to antitoxin therapy and in the treatment of the carrier state.

In general, early acute bacterial infections respond more rapidly to penicillin therapy than do subacute or chronic states. However, penicillin does have an important role in prophylaxis. The drug has been used successfully prophylactically in the prevention of gonorrhea, surgical infections, suspected streptococcal infections, and rheumatic fever.

### Dosage.

In acute infectious diseases, penicillin must be administered in a dosage form suitable to achieve adequate blood and tissue concentrations. As will be pointed out, many factors influence the distribution of the drug in the body; however, certain general statements can be made regarding penicillin dosage. Because there are so many varieties of penicillins and so many dosage forms, the only true guide to correct dosage is the manufacturer's suggested dose and the physician's clinical experience.

**Injection for prolonged action.** The drug is usually administered by intramuscular injection, for prolonged action. A single dose of 300,000 units of procaine penicillin G once every 12 to 24 hours is usually adequate in most infections caused by penicillin-susceptible organisms. Benzathine penicillin G gives a more prolonged blood level. Procaine penicillin G with aluminum stearate suspended in peanut or sesame oil provides an intermediate action. About 60 hours after an injection of 300,000 units of this latter form of penicillin, one may still detect blood levels.

**Injection for prompt action.** For prompt absorption and a rapid rise in the blood penicillin concentration, the potassium or sodium salt of penicillin G dissolved in sterile distilled water, isotonic saline, or 5 per cent dextrose solution is employed. This solution may be injected intramuscularly, subcutaneously, or intravenously. The usual dose is from 100,000 to 600,000 units. Because this salt form is rapidly absorbed and rapidly excreted, the injection must be repeated every 3 to 4 hours in order to maintain effective blood concentrations. Continuous intravenous infusion is employed in severe infections, and penicillin is administered in these cases as a solution containing 25 to 50 units per ml. at a rate of 5,000 to 10,000 units per hour. In severe fulminating infections, as in *bacterial endocarditis,* 600,000 units administered every 6 hours are considered necessary.

Subcutaneous injections of penicillin are subject to erratic absorption and are not used in the treatment of systemic infections. In the treatment of infections of a superficial and restricted nature, the solution may be injected subcutaneously to provide a local concentration of penicillin.

Because penicillin does not appreciably penetrate the subarachnoid space, intrathecal or intracisternal injections are employed in the treatment of meningitis. A total daily dose of 10,000 to 20,000 units is used, and the penicillin concentration is not to exceed 1,000 units per ml. This type of therapy is hazardous because penicillin is toxic to the tissues of the central nervous system.

The recommended dosage schedule in prophylaxis of rheumatic fever and the control of streptococcal infections in bacterial endocarditis is monthly intramuscular injections of 1,200,000 units of benzathine penicillin G. If oral prophylaxis is chosen, the recommended dose is 200,000 to 250,000 units twice daily.

Evidence is now available which indicates that over the past decade strains of *N. gonorrheae* isolated from infected subjects have decreased in their sensitivity to penicillin. A very long-acting variety of penicillin is desirable, and benzathine penicillin G seems to be adequate in this respect. A single 300,000-unit dose intramuscularly is enough to effect a cure in most cases.

Troches of penicillin containing from 1,000 to 20,000 units of the calcium salt are used in infections of the mouth and throat caused by Vincent's organism and other penicillin-susceptible infections of the mouth. Because of the danger of sensitization to penicillin, local application of the antibiotic should be severely limited, and some authorities insist that the drug should never be used locally, for this encourages the development of resistant strains of bacteria.

**Oral administration.** Penicillin G may be administered orally in doses of from 3 to 6 times the amount usually recommended for injection. Compressed, uncoated tablets containing 50,000 to 100,000 units of penicillin G calcium, sodium, or potassium with 0.5 gm. of trisodium citrate or calcium carbonate in each tablet is a common dosage form. Oral doses of penicillin should be given between meals.

It was thought at one time that it was necessary to protect penicillin from the destructive action of the hydrochloric acid of the stomach when the drug was taken orally. The successful use of unbuffered oral penicillin preparations leads one to conclude that this view is not entirely correct. The introduction of phenoxymethyl penicillin V confirms this concept. Phenoxymethyl penicillin V is a stable oral dosage form of penicillin.

The insolubility of the aluminum salt of penicillin in the hydrochloric acid of the stomach is said to make this salt available for oral use. Tablets of aluminum penicillin, 50,000 units, with 0.3 gm. of sodium benzoate, are commercially available.

Benzathine penicillin G is administered orally. Tablets containing 100,000 and 200,000 units per tablet and an oral suspension of 30,000 and 60,000 units per ml. are prepared for clinical use.

**Penicillin inhalation therapy.** An aerosol of penicillin prepared by nebulizing a solution of penicillin has been found to be useful in the treatment of chronic and acute pulmonary infections. Penicillin dusts administered by inhalation have likewise been employed with success in treating a variety of upper respiratory tract infections.

Penicillin liquid aerosols or dusts may be of value when combined with systemic administration. A higher concentration of the drug is produced at the site of the infection. Inhalation therapy is not to be used in lieu of systemic medication in acute infections. The possibility of sensitivity reactions, especially in patients with asthma, enjoins special caution in this route of administration. Dusts are more likely to produce bronchospasm than aerosols. For this reason inhalation therapy with penicillin should be employed only in carefully selected patients.

**Local application.** Penicillin G may be applied locally in solution or powder form or as an ointment. Its use in this manner should be predicated upon bacteriologic diagnosis, in which the infecting organism is known to be susceptible to the drug. The sodium salt is considered too irritating for local use. Penicillin G calcium in a nonirritating ointment base is used in the treatment of superficial infections of the eye, particularly those affecting the cornea, conjunctiva, and lacrimal sac, caused by penicillin-susceptible organisms.

**Penicillin-resistant infections.** A problem of increasing importance is the development of penicillin resistance by staphylococci and certain varieties of coliform microorganisms. This acquired resistance appears to be related to the wide use of the antibiotic. It has been pointed out by many workers that the problem of penicillin-resistant micrococci arises most frequently in hospitalized patients. The percentage of penicillin-resistant strains of *M. pyogenes* var. *aureus* isolated from patients in large hospitals in various parts of the world has increased during recent years. The evidence indicates that patients acquire the penicillin-resistant micrococci after admission to the hospital. The incidence of penicillin-resistant micrococci among outpatients is much lower.

There is little evidence that a majority of the common pathogenic organisms other than micrococci have increased their resistance to penicillin. No significant increase in resistance has been reported among strains of *hemolytic streptococci, pneumococci, Hemophilus influenzae*, and *meningococci*. The prevalence of penicillin-resistant micrococci does not mean that all types of microorganisms will eventually become resistant to the antibiotic.

The most difficult problem is the control of staphylococci that produce penicillinase and are therefore resistant to penicillin G. The most recently discovered varieties of penicillin fortunately seem superior in this respect. For example, methicillin is not inactivated by penicillinase to an appreciable degree; consequently, it is effective against staphylococci no matter how much penicillinase they produce (Dowling, 1961). Oxacillin is indicated solely for infections with penicillinase-forming staphylococci. These latter drugs are not to be used routinely but should be retained for those cases presenting penicillin G-resistant staphylococcic infections.

**The significance of penicillin blood levels.** Formerly, penicillin blood levels were determined as a guide for dosage. At the present time, the clinical response of the patient is generally used as an index of adequate dosage. It is preferable to overdose rather than to risk the possibility of the development of drug fastness.

A penicillin blood serum level of 0.3 unit per ml. or greater is considered necessary to combat most infections. This concentration can be provided by an intramuscular injection of 300,000 units of procaine penicillin G. In addition, this dosage form will provide an effective blood level for 8 to 12 hours.

Several aspects of the relationship of dosage of penicillin to blood serum levels require special comment. Penicillin, while not inhibited in its anti-bacterial action by serum, is adsorbed to a considerable degree on serum protein. Particularly is this true for penicillin K. Such bound penicillin may not be measured by the analytical procedure generally employed, but it is therapeutically inactive.

The rate of killing of susceptible microorganisms is not increased by increasing the blood level of penicillin. A maximal rate of destruction is achieved by the usual recommended doses. This demonstrates that massive doses of penicillin do not kill invading organisms faster and that single large doses of a variety of short-acting penicillins may be relatively ineffective. The maintenance of blood concentrations for adequate time periods is necessary for cure of the infection. Therapeutic blood levels may be greater than 0.3 unit per ml., but these do not necessarily insure a faster cure rate.

The question of the most efficient dosage schedule for penicillin is complicated by the lack of a chemical method for determining the concentration of penicillin in plasma and body fluids. What is determined in the microbiologic assay is the bacteriostatic activity of the body fluid resulting from the administration of the antibiotic. This might be termed more properly the *acquired bactericidal property*. It is well recognized, but frequently overlooked, that serum and body fluids possess some anti-bacterial activity in the absence of an antibiotic.

**Penicillin allergy.**

Untoward reactions following the parenteral injection of penicillin have been chiefly *allergic hypersensitivity* of a generalized nature or local *sensitivity reactions*. These may occur at once or within a week or two after treatment is discontinued. The reaction is not related to the dose administered. Ten to twenty times the usual therapeutic dose of penicillin may be administered with impunity in insensitive patients.

Symptoms of hypersensitivity may be urticaria, contact dermatitis, periorbital or labial edema, drug fever, gastrointestinal reactions, headache, eosinophilia, edema of the hands, faintness, skin flushing or pruritus, generalized arthralgia, myalgia, and malaise. Conditions resembling those of serum sickness have been reported. Fatal anaphylactic reactions may follow the intramuscular injection of penicillin. Fatal exfoliative dermatitis is a rare reaction. The prognosis is very grave if an individual who is sensitive to penicillin has received a long-action dosage form of the drug.

Elimination of the impurities in penicillin has demonstrated that crystalline forms induce a true sensitivity in susceptible individuals. Conservative reports place the incidence of allergy to crystalline penicillin G between 0.5 and 3 per cent of all patients treated. Sensitivity phenomena have been reported to occur in approximately 6 per cent of general medical patients receiving penicillin in some form. An incidence of approximately 25 per cent has been found in dermatologic patients. Hypersensitivity to penicillin is most apt to occur in persons who have some other form of allergy or who have previously been treated with penicillin. A history of penicillin sensitivity necessitates great caution in the further use of the drug. It has been reported that the incidence of penicillin sensitivity is about equal in adults of both sexes, and that children of both sexes under 12 years of age are more resistant than adults.

Epidermal sensitization to penicillin has been found to be transient. While the immediate reactions may be disturbing or even alarming to the patient, they are usually of short duration and subside upon withdrawal of the drug. Some clinicians have observed that the continuance of the penicillin was accompanied by a decrease in the severity of the reactions within 4 to 5 days. Antihistaminic compounds have produced a spectacular relief of the symptoms of penicillin reactions. Penicillinase (see page 90) has been used in the treatment of sensitization reactions to penicillin.

Penicillin is widely used by dairy farmers in the treatment of mastitis in cows. If milk containing penicillin from these animals is consumed by persons who are allergic, or who may be sensitized by exposure to small, variable amounts of penicillin, the subsequent use of the antibiotic for medical needs may elicit allergic reactions. Indeed, the continued use of penicillin-contaminated milk presumably is capable of producing immediate or delayed generalized allergic reactions (Carr and Aste, 1961).

**Fatal anaphylactic reactions.** There is evidence that a true atopic or anaphylactic type of sensitivity may develop in persons as a result of repeated administration of penicillin. Apparently circulating antibodies to this drug are produced, and an immediate whealing skin reaction to a scratch test may be detected in such persons. This simple but hazardous means of detecting hypersensitive individuals should make severe or fatal anaphylactic reactions preventable. However, the use of sensitivity tests prior to the injection of penicillin has never been widely practiced.

Levine (1963) has demonstrated that the benzylpenicilloyl group is the major antigenic determinant of hypersensitivity to benzylpenicillin in human beings and experimental animals. This observation has provided a new kind of sensitivity skin test. The suspected subject is not injected with the sensitizing agent, as in most sensitivity tests. The use of a synthetic polymer, penicilloyl-polylysine, elicits skin responses in persons with penicillin sensitivity, yet the reaction does not stimulate the development of hypersensitivity—a possible danger in diagnostic testing.

Rytel *et al.* (1963) demonstrated the value of penicilloyl-polylysine technic in naval recruits administered benzathine penicillin G prophylactically to prevent rheumatic fever. Over 1000 men aged 17 to 18 years were given skin tests by these investigators, who found a 35 per cent incidence of positive skin reactions among individuals allergic to penicillin, as compared to an incidence of 6.8 per cent in nonallergic recruits.

A strong positive skin test implied an almost nine times greater risk of occurrence of a systemic reaction following penicillin treatment.

Welch (1957) surveyed serious antibiotic reactions reported between 1953 and 1957. Penicillin was incriminated in 900 of 1070 cases classified as life-threatening; there were 809 instances of anaphylactoid shock (of which 72 resulted in death), 70 severe skin reactions, 46 blood dyscrasias, and 38 cases of angioneurotic edema. In a more recent survey in 1958, he concluded that a mortality of approximately 10 per cent was experienced in 793 cases of anaphylaxis caused by penicillin reported over a 3-year period. Anaphylactic reactions usually occur after the intramuscular administration of procaine penicillin G. The reported figures of fatalities are low, and many cases are unreported. Early recognition of an anaphylactic reaction and immediate treatment with hypodermically administered epinephrine solution may be lifesaving.

The majority of persons who have had anaphylactic reactions had received a number of injections of penicillin. However, according to some reports, such a reaction may follow the first time the drug is administered (Carr and Aste, 1961). The severe reaction is usually very rapid in onset and occurs within a few seconds or several minutes after penicillin injection. Shock associated with a serious fall in blood pressure is the most significant change. Slow, labored breathing and cyanosis followed by unconsciousness have occurred in most cases of this type. Some individuals have experienced convulsions. Death has followed within several minutes to 2 to 4 hours, and appears to result from either shock or asphyxia. Thirty cases of anaphylactic shock, with 3 deaths, have been reported following oral doses of penicillin (Wirth, 1963).

*The recognition of serious toxic reactions to penicillin enjoins caution in the promiscuous use of the drug.* The best method of preventing situations in which the patient is allergic to penicillin at a time when it is sorely needed is not to give the drug if it is not absolutely required. The use of penicillin and other antibiotics for trivial infections should be severely criticized, and such practices should be discouraged.

### STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

Streptomycin is an antibiotic, first isolated from *Streptomyces griseus* by Schatz, Bugie, and Waksman in 1944. It is active against certain gram-negative and gram-positive organisms, including acid-fast bacteria.

Streptomycin was the first antibiotic of practical significance to be isolated from the class of organisms known as *Actinomycetaceae.* This family of organisms differs from the mold that produces penicillin or the bacterium that yields tyrothricin. Actinomycetes grow as branching rods that may form filaments; they are smaller than the filaments of *Penicillium.* Waksman described *S. griseus* in 1915.

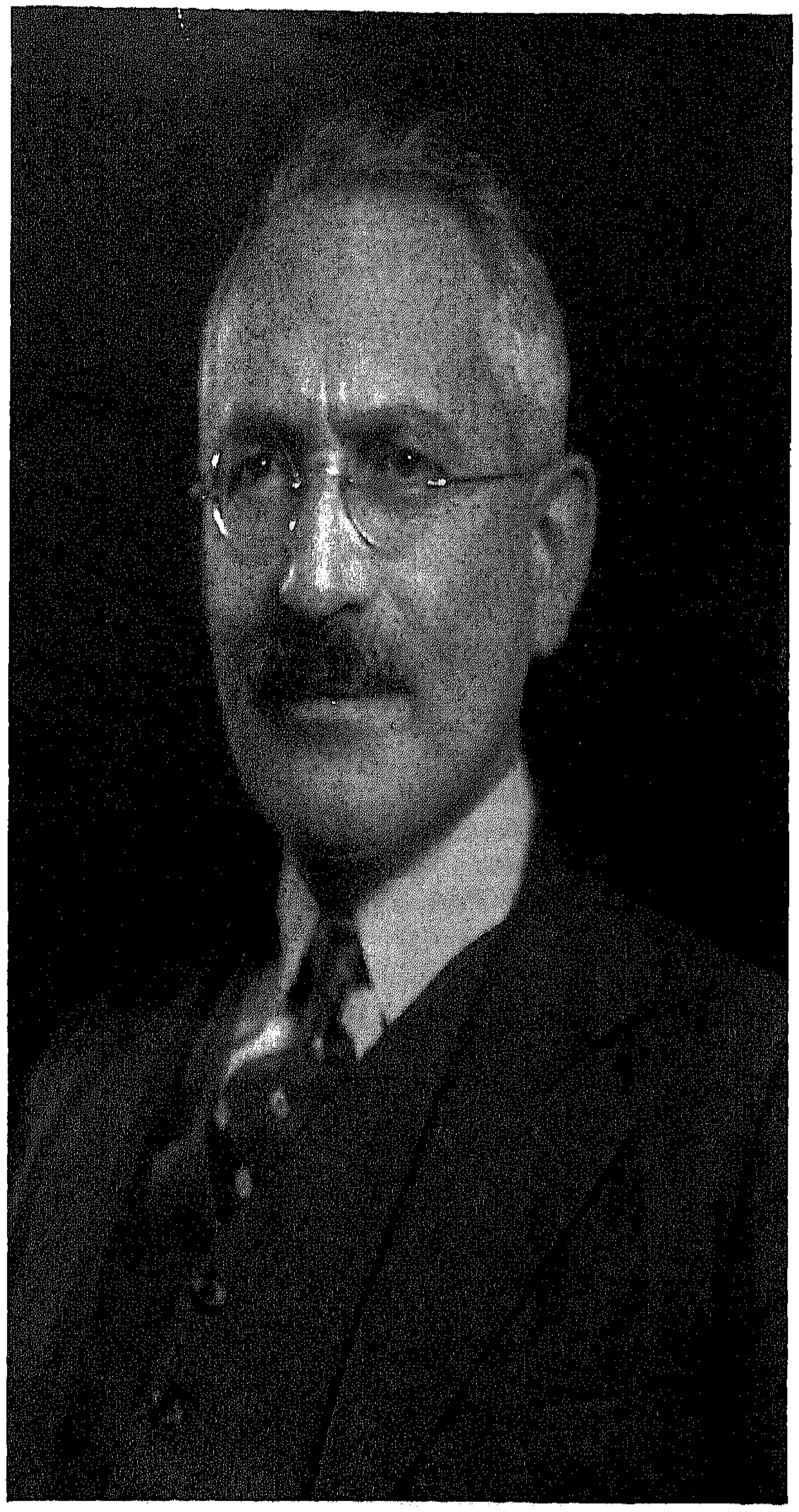
### Antibiotics from Actinomycetaceae.

Shortly after its discovery, streptomycin was observed to be active against the *Mycobacterium tuberculosis.* It has been established that the production of tuberculostatic agents is widespread among many classes of microorganisms, the fungi, bacteria, and actinomycetes. Among the fungi, the *Aspergillus fumigatus* group produces *fumigacin.* Among the bacteria, the *Bacillus subtilis* group produces *subtilin.* The actinomycetes have served as the source of several antibiotics active against *M. tuberculosis,* namely, actinomycin, streptothricin, streptomycin, and neomycin. In addition, cycloserine (Seromycin) obtained from *Streptomyces orchidaceus,* identical with Oxamycin from *S. garyphalus,* is effective in tuberculosis.

The potential value of the *Actinomycetaceae* family as a source of other useful antibiotic drugs is illustrated by the discovery of novobiocin and vancomycin, effective against staphylococci, from *S. spheroides;* chloramphenicol from *S. venezuelae;* and actinomycin-C, possessing antitumor activity, from *S. chrysomallias.* The broad-spectrum antibiotics chlortetracycline, oxytetracycline, and erythromycin are also obtained from streptomyces species. Over 400 antibiotic substances have been isolated from actinomycetes species; of these, approximately 30 have had some chemotherapeutic application. The names, descriptions, and properties of these antibiotics have been reviewed by Waksman and Lechevalier (1962).

### Chemical nature.

Streptomycin is an amino base and forms salts which are very soluble in water; the sulfate and the calcium chloride double salt are white, amorphous powders. The molecule contains 2 strongly basic guanido groups and a weakly basic methylamino group. Streptomycin is a glucoside and on acid hydrolysis yields *streptidine* and *streptobiosamine.* The structure of streptidine is that of inositol, in which 2 hydroxyl groups are replaced by guanido groups. Streptobiosamine is a disaccharide composed of N-methyl-1-glucosamine and 4-methyl-1-tetrose, in which a hydrogen atom at position 3 is replaced by an aldehyde group. Dihydrostreptomycin is prepared by catalytic hydrogenation of the aldehyde group at position 3 with the formation of a $-CH_2OH$ group.

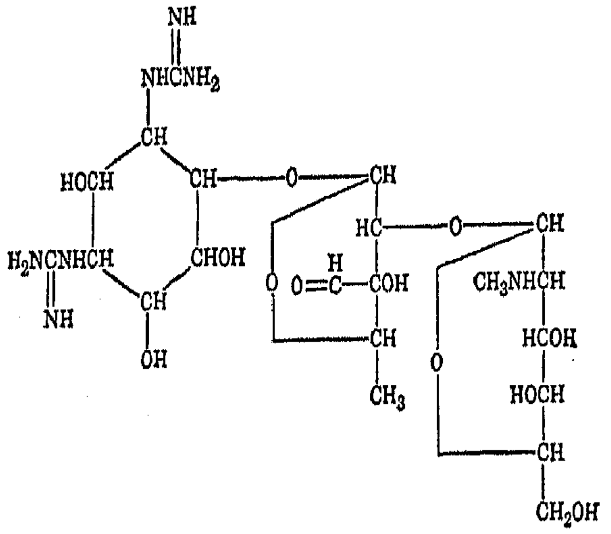


SELMAN A. WAKSMAN

*Investigator in the field of antibiotics; the discoverer of streptomycin*

"The ability of an antagonist or its products—antibiotic substances—to destroy a parasitic microorganism *in vivo* is influenced by the nature of the host as well as by the type and degree of the infection."

**Streptomycin Sulfate, U.S.P.** Streptomycin sulfate is odorless, or nearly so, and has a slightly bitter taste. It is hygroscopic and may deliquesce on exposure to air.



Streptomycin, U.S.P.

Streptomycin sulfate in the form of the dry powder may be stored in the original unopened container at room temperature for 2 years. Aqueous solutions should be refrigerated under aseptic conditions. Potency is maintained under these conditions for one week. Solutions having a pH lower than 4 or higher than 7 are less stable. Solutions of streptomycin should not be autoclaved, since a considerable loss of potency will ensue. Only freshly prepared solutions should be injected parenterally.

**Dihydrostreptomycin Sulfate, U.S.P.** Dihydrostreptomycin sulfate occurs as white or faintly yellow granules or a white powder. Dihydrostreptomycin sulfate is supplied as the dry powder in 2- and 20-ml. vials containing the equivalent of 1 or 5 gm. of streptomycin base, respectively.

The anti-bacterial spectrum of dihydrostreptomycin is very similar to that of streptomycin. Those strains of bacteria that have developed resistance to streptomycin are also resistant to dihydrostreptomycin. Inactivators for streptomycin, *e.g.*, cysteine or mild alkali, do not inactivate solutions of dihydrostreptomycin.

Dihydrostreptomycin and streptomycin are effective against the same pathogenic microorganisms; therefore, they have essentially the same therapeutic uses. Dihydrostreptomycin is used only by intramuscular injection. *It must not be injected intravenously.*

### Anti-bacterial spectrum.

Since the antibacterial spectra of dihydrostreptomycin and streptomycin are the same, these two antibiotics will be considered together in a generic sense. Streptomycin is active against a wide variety of gram-negative organisms, including *E. coli*, *Pseudomonas aeruginosa*, *Pasteurella tularensis*, *Hemophilus influenzae*, *Mycobacterium tuberculosis*, and *Eberthella typhosus*. Streptomycin also effectively inhibits the growth of a variety of gram-positive organisms. Clinically, however, it is not ordinarily employed against these pathogens. In table 10-2 the principal microbial diseases amenable to streptomycin therapy are listed. Unfortunately, susceptible microorganisms rapidly develop resistance to streptomycin. For this reason its use should be based upon laboratory evidence of the susceptibility of the strain of infecting microbe.

### Assay.

Biologic assays of streptomycin are similar to those employed in assaying penicillin. Standardized strains of *E. coli* or *B. subtilis* are commonly used as the test organisms.

Chemical methods of assay are also available for streptomycin. Generally they are preferable to microbiologic methods because of greater accuracy and specificity. The fluorometric method for the determination of streptomycin in blood and spinal fluid is based on the presence of the reactive carbonyl group together with the strongly basic groups in one molecule. The method is capable of detecting 1 mcg. of streptomycin. Another method has been developed, based on the formation of a colored semicarbazone by reaction of streptomycin with a highly colored semicarbazide. The former method is more sensitive, while the latter is more rapid and does not require a fluorophotometer.

### Inactivation.

Streptomycin, unlike penicillin, is not inactivated by bacterial enzymes. Ascorbic acid and sulfhydryl compounds, *e.g.*, cysteine and thioglycolate, are antagonistic substances. Anaerobic conditions in the medium or a low pH will reduce the potency of streptomycin. The activity of streptomycin antagonists has given rise to theories of action of this antibiotic.

### Toxicity.

A distinction must be made between the toxicity of streptomycin and that of dihydrostreptomycin. Pure streptomycin injected intravenously in dogs in doses from 100 to 200 mg./kg. of the base causes a gradual fall in blood pressure. Larger doses (200 to 400 mg./kg.) produce an irreversible lowering of the blood pressure. If death follows despite artificial respiration, it is probably caused by a paralysis of the vasomotor centers. Electrocardiograms taken following the injection of very large doses of streptomycin show no significant changes.

The most prominent pharmacodynamic property of streptomycin or dihydrostreptomycin is the neurotropic effect. In animals this effect can be produced by repeated subcutaneous, intramuscular, or intravenous injections of from 50 to 400 mg./kg. of pure streptomycin base. The characteristic effects in animals are a change of gait and posture, ataxia of the hind legs and later the forelimbs, and a progressive loss of rotational nystagmus. In man, the inability to keep the eyes focused on a given spot causes difficulties in reading. This is believed to be the result of a disturbance in the vestibular apparatus. Closely related cerebellar and oculomotor functions may also be involved. Ataxia and hearing defects in man may be quite marked and long lasting. Audiometric and vestibular function tests may be conducted on individuals about to receive streptomycin therapy in order to detect the first appearance of toxicity.

Dihydrostreptomycin is less toxic than streptomycin to the vestibular apparatus and more toxic to auditory function. Streptomycin is more likely to cause vertigo than dihydrostreptomycin but less likely to cause hearing impairment. Since vestibular disturbances are less serious than cochlear function, streptomycin is the drug of choice for prolonged medication. Because streptomycin is as effective as dihydrostreptomycin and the toxic reactions from streptomycin occur immediately and are more easily recognized and less permanently disabling, there seems to be little reason to use the more dangerous drug.

Common untoward effects encountered in clinical practice following streptomycin have been severe headache, anorexia, nausea, abdominal pain, eruptions of the skin, generalized arthralgia, fever, and pain at the site of injection. Agranulocytosis has been reported after streptomycin therapy.

Allergic urticarial reactions following streptomycin therapy may be localized or they may be distributed over the entire body. Persons who handle this antibiotic may develop a contact dermatitis.

### Absorption, distribution, and excretion.

Streptomycin is rapidly absorbed after intramuscular injection and maximal blood levels are attained in from 1 to 3 hours. It appears in the urine in amounts from 60 to 80 per cent of the total dose within 24 hours. For the maintenance of therapeutic blood levels, injections are repeated at 6-hour intervals.

Oral administration of streptomycin is of no value in the treatment of systemic infections; it is not appreciably absorbed, although, unlike penicillin, it is not significantly decomposed in the stomach or intestines.

Streptomycin is not found in the cerebrospinal fluid following parenteral administration. Intrathecal as well as intramuscular injection is considered necessary in bacterial tuberculous meningitis. Intrathecal administration may be used when high concentrations of streptomycin in the cerebrospinal fluid are desired. In the presence of meningitis large doses given by intramuscular injection result in cerebrospinal fluid concentrations approximately ⅙ of those in the blood. In patients not suffering from meningitis, the diffusion of streptomycin into the cerebrospinal fluid does not take place readily.

Following parenteral injection, streptomycin is present in effective concentrations in ascitic, peritoneal, and pleural fluids. It is excreted in the bile, milk, saliva, sweat, and tears.

### Mechanism of action.

While the mechanism of action of streptomycin against bacteria remains obscure, a number of investigations have demonstrated that this antibiotic interferes with normal cellular division. Transmission electron micrographs have shown the effect of streptomycin upon *K. pneumoniae.* After 18 hours' exposure to the antibiotic solution, the organisms exhibit a typical elongation. Cell growth continues, but normal cellular division is inhibited. The bactericidal action of streptomycin under these conditions is related to cellular disintegration.

The mechanism of action of streptomycin against bacteria appears to be fundamentally different from that of penicillin. The differences in their antibiotic spectra suggest different mechanisms of action. Streptomycin can precipitate as a complex with desoxyribonucleic acid. This fact suggests an interference with protein synthesis. Streptomycin intervenes in ribonucleic acid metabolism by blocking a reaction preceding the formation of mononucleotides. It has been shown to inhibit the oxidation of ribonucleic acid with some organisms; however, these reactions are not found to occur with all microorganisms sensitive to the drug. A number of antibacterial agents, including streptomycin, are capable of combining with certain thiols in isolated chemical systems. Combination with thiol groups may mediate the anti-bacterial action of these drugs. Streptomycin is inactivated by cysteine, hydroxylamine, and semicarbizide; this may be related to the mechanism of action of the antibiotic. These agents are employed to inactivate the antibiotic in order to demonstrate the presence of infecting organisms in sterility testing and blood culture studies. No bacterial enzyme similar to penicillinase has been found that will inhibit streptomycin or dihydrostreptomycin (Gale, 1963).

The studies of Umbreit and his colleagues have indicated that streptomycin interferes with the reaction between pyruvate and oxalacetate in cell metabolism. This system controls the variety of substances entering the terminal respiration system. It is important to bacterial cells as well as to animal tissue cells. It has been suggested that a permeability barrier exists at the animal cell wall that prevents streptomycin from penetrating to the site of the mitochondria. In the bacterial cell, the reaction system is not so protected, and hence the metabolic function of the cell is interrupted. This concept has been substantiated by the finding that streptomycin prevents the formation of a new metabolic intermediate that is normally formed in bacteria when pyruvate and a 4-carbon dicarboxy acid are present. This may explain the difference in toxicity to bacterial cells and animal cells, Umbreit (1953 *et seq.*). Subsequently, Johnston (1962) demonstrated that streptomycin is inhibitory to ergosterol synthesis in growing cultures and cell-free preparations of yeasts. This supports the theory that the prime action of streptomycin is to prevent the utilization of the phosphorylated 4-carboxy adipic acid in the biosynthesis of sterols, as proposed by Umbreit. The most prominent effect is an inhibition of protein synthesis.

Like penicillin, streptomycin exerts its effects on tubercle bacilli when they are in a growing rather than in a resting phase. This suggests that the process of division, with its rapid synthesis of bacterial cell constituents, is blocked by the drug. This observation is in accord with the recognized failure of streptomycin to clear old dormant tuberculous lesions where the bacilli are presumably in a resting state. Hobby and Lenert (1957) proposed that streptomycin may be bacteriostatic or bactericidal, depending upon the stage of microbial growth or resting patterns. In fact, two separate mechanisms may be involved.

### Therapeutic use.

Investigations have revealed the clinical value of streptomycin in a wide variety of gram-negative infections. It has proved to be dramatically effective in tuberculosis, tularemia, and plague. The selection of streptomycin as the anti-bacterial agent of choice is indicated in table 10-2.

Various species and strains of bacteria vary widely in their sensitivity to streptomycin. It is imperative that careful bacteriologic studies be made before and during treatment with streptomycin. The recognition of a susceptible strain of organism is important. *It is a cardinal rule of streptomycin therapy that this drug should not be administered to a patient if the organism causing the disease has not been identified.* Dosage is dependent upon the etiology of the disease process, the locus of the infection, and the ability of the drug to reach the site of the bacterial invasion. Some authorities recommend that streptomycin is to be used only in tuberculosis. Others feel that this antibiotic is indicated in infections only where the invading organism is definitely streptomycin-susceptible.

Streptomycin has been reported to be of limited value in staphylococcic endocarditis caused by penicillin-resistant but streptomycin-susceptible organisms. In bacillary meningitis, bacteremia, and systemic infections caused by a variety of susceptible bacteria, streptomycin has been effective in saving the life of the patient.

The therapeutic use of streptomycin in tuberculosis is discussed in Chapter 11.

**Dosage and route of administration.** In the treatment of systemic infections, intramuscular injections are required. Intrathecal, intrapleural, intraperitoneal, subcutaneous, and topical administration is also employed. Inhalation of an aerosol may be indicated in special cases.

Individual doses vary, depending upon the severity of the infection and the sensitivity of the organism to the drug. The objective is to bring the infection under control as *quickly* as possible. In some cases the organisms develop resistance to streptomycin with extreme rapidity. Drug fastness is an ever-present possibility with streptomycin therapy. For very severe fulminating infections it may be necessary to administer from 2 to 4 gm. per day in divided doses every 6 to 12 hours. Generally, smaller doses are employed; a dose of 1 to 2 gm. administered daily is considered adequate in less severe infections. To prepare the solution of streptomycin for intramuscular injection, the powder is dissolved in sterile distilled water or isotonic sodium chloride solution to give a solution of 100 to 200 mg./ml. of streptomycin base. Streptomycin dosage is continued for at least a week after the temperature has returned to normal.

For intrathecal administration, from 25 to 100 mg. of streptomycin dissolved in 5 to 10 ml. of sterile isotonic sodium chloride solution may be injected after the withdrawal of the proper volume of spinal fluid. Intermittent intramuscular injections are employed concurrently to maintain effective drug levels in the blood.

Dihydrostreptomycin is not administered intrathecally or intravenously. It is administered by intramuscular injection in doses equal to those of streptomycin. Dihydrostreptomycin sulfate solutions are prepared to contain 250 to 500 mg./ml. of the base. Only freshly prepared solutions should be used, and the volume injected at a single site should not exceed 2 ml. Dihydrostreptomycin should not be used except in critical situations where no other antibiotic can be employed.

**Blood level.** For the treatment of systemic infections, adequate blood concentrations are necessary. It is important to interpret blood values in terms of whole blood or serum. Streptomycin does not penetrate the erythrocytes, so that the concentration in the serum is approximately twice that in whole blood. When streptomycin is injected parenterally, the serum streptomycin concentration rapidly reaches a peak and then slowly decreases. The declining slope of the curve indicates a permissible interval of from 4 to 6 hours between doses. It is possible to maintain a therapeutic blood concentration by the injection of 2 to 3 gm. intramuscularly, with a resulting blood level between 20 and 60 mcg./ml. The blood level is largely controlled by urinary excretion, and this factor will vary widely in different patients.

With streptomycin the hazards of drug resistance and the wide variation in threshold susceptibility of different organisms indicate the need for a flexible dosage schedule adapted to each patient. Since bacterial infections resistant to streptomycin are difficult to control even with a substantial increase in dosage, the clinical progress of the patient should be watched closely. This can be done best by the determination of the streptomycin sensitivity of the organism and the concentration of the drug in the blood.

### Viomycin

**Viomycin (Viocin, Vinactane)** is an antibiotic produced by *Streptomyces puniceus*. It was first isolated in 1951 and shown to be active against various strains of *M. tuberculosis*.

Viomycin is prepared as a purified product as its sulfate. It is a strongly basic polypeptide of unknown chemical structure. The sulfate is a white or slightly yellow odorless powder. The sterile powder readily dissolves in water or isotonic saline solution. In the form of the dry powder it may be stored at room temperature for two years without appreciable loss of potency.

The drug is administered intramuscularly exclusively in tuberculosis therapy. Effective blood levels can be demonstrated after parenteral injection, and a small amount of the antibiotic diffuses into the spinal fluid and peritoneal cavities. Viomycin should not be injected intravenously. It is ineffective by oral administration.

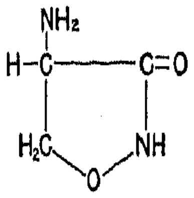
The activity of viomycin against the virulent human strains of *M. tuberculosis* and streptomycin-resistant forms of tubercle bacilli is noteworthy. The antibiotic is not as active as streptomycin, but cross-resistance apparently does not develop. The use of this drug in tuberculosis chemotherapy is discussed in the following chapter.

Viomycin is used in the treatment of tuberculosis in much the same manner as streptomycin. The antibiotic produces eighth nerve damage and may impair kidney function. It is excreted by the kidneys, and for this reason renal function should be normal in candidates for viomycin therapy. Allergic reactions and serum electrolyte imbalance have been observed following administration of the antibiotic. The incidence of side effects can be reduced if the dose does not exceed 2 gm. of the base intramuscularly every 3 days.

Viomycin sulfate is supplied as a sterile powder in vials containing an equivalent of 1 and 5 gm. of viomycin base.

### Cycloserine

**Cycloserine (Seromycin, Oxamycin)** is a crystalline broad-spectrum antibiotic made by fermentation with *Streptomyces garyphalus* or *S. orchidaceus* or by synthesis. It is D-4-amino-3-isoxazolidone.



Cycloserine

Cycloserine is effective orally. It is active against gram-positive and gram-negative organisms, the rickettsiae, some protozoa, and *M. tuberculosis*. Cycloserine exhibits a synergistic action with penicillin, the tetracyclines, and bacitracin.

Cycloserine exhibits a relatively low toxicity in experimental animals. It is rapidly absorbed after oral administration, and significant levels are obtained in the blood, urine, lymph, amniotic fluid, cerebrospinal fluid, and aqueous humor. A large portion of the ingested drug is recovered in the urine.

Cycloserine is a weak but effective antituberculosis agent. It is absorbed readily after oral doses, and therapeutically effective blood levels can be attained within 4 to 8 hours after administration. It has a relatively minor role in tuberculosis chemotherapy, in the treatment of those patients who fail to respond to other drugs. Its use in tuberculosis therapy is discussed in Chapter 11.

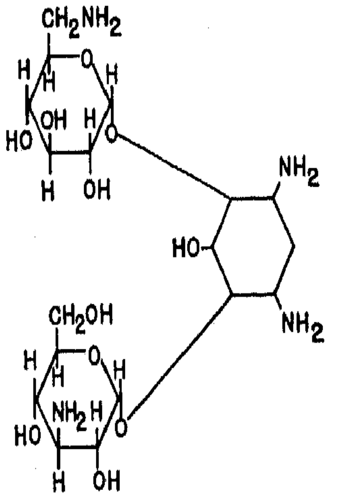
Cycloserine-resistant strains of microorganisms do develop with therapy; however, the speed of emergence varies; the toxicity of the drug must be weighed against this fact in selecting the optimal dose. Cycloserine has been used in the treatment of urinary tract infections of streptococci, staphylococci, *E. coli*, and *A. aerogenes*. It has been reported to be useful in *Nocardia asteroides* infections in the lungs of patients allergic to sulfonamides, the drugs of choice in this disease.

The toxicity of cycloserine may pose serious problems. These are discussed in the consideration of the drug in the treatment of tuberculosis.

The usual dose is 0.5 gm. per day orally. This dose or less may be combined with other drugs in the treatment of tuberculosis. Initially, the drug should be administered orally only to hospitalized patients under close observation, and blood levels of the drug must be used as a guide to proper dosage. Cycloserine is available in the form of 250-mg. capsules.

### Kanamycin

**Kanamycin Sulfate, U. S. P. (Kantrex)** is produced by a soil organism *Streptomyces kanamyceticus* as a water-soluble basic substance. It was isolated as a crystalline sulfate in 1957. The molecule of kanamycin resembles streptomycin. It is made up of two amino sugars, 6-amino-6-deoxy-D-glucose, and 3-amino-3-deoxy-D-glucose, linked glycosidically to 2-deoxystreptamine.



Kanamycin

Although originally isolated as an antibiotic active *in vitro* against *M. tuberculosis* and subsequently demonstrated as effective *in vivo* in experimental tuberculosis in guinea pigs, kanamycin did not prove to be as effective as streptomycin in chemotherapeutic trials. Its toxicity limits its usefulness. The anti-bacterial spectrum of kanamycin is almost identical with that of neomycin, and microbial cross-resistance exists between the two antibiotics. Although active against many gram-positive and gram-negative bacteria, clinical usefulness of kanamycin is generally limited to severe infections with gram-negative organisms, *e.g.*, gram-negative rods of the urinary tract, *Klebsiella-Aerobacter* organisms and strains of *Proteus* and *Pseudomonas*. The drug is believed to be bactericidal.

Kanamycin is not absorbed when given orally and is therefore administered by intramuscular injection. It is rarely given intravenously. The sulfate salt is a water-soluble form suitable for injection.

In several species of animals kanamycin is somewhat less acutely toxic than streptomycin. In dogs, intravenous doses of less than 200 mg./kg. elicited a fall in blood pressure, and a dose of 250 mg./kg. produced respiratory paralysis. Kanamycin is less nephrotoxic than neomycin in dogs. In man, kanamycin frequently produces renal injury, but the effects are reversible when the drug is stopped. In patients with renal disease renal failure may be produced, with severe nitrogen retention and oliguria which compels discontinuance of the drug. Auditory damage is the most serious toxic effect of kanamycin (Tisch *et al.*, 1958).

*In vitro* and *in vivo* resistance to kanamycin can be demonstrated for sensitive microorganisms. Organisms made resistant to kanamycin are also resistant to streptomycin; however, bacteria made resistant to streptomycin are sensitive to kanamycin.

Kanamycin sulfate is available in 500-mg. capsules and as an injection, 0.5 gm./2 ml. and 1 gm./3 ml.

Kanamycin is injected intramuscularly in adults in doses of 15 mg./kg. daily in 2 or 3 divided doses for not more than 14 days. In patients with renal disease and impaired renal function, the daily dose should be reduced to avoid accumulation of the drug in the serum or tissues. A pretreatment audiogram is a wise precaution to allow comparative tests during therapy, especially if the drug is to be administered for 7 days or more. The therapy should be stopped if tinnitis or hearing loss develops. Almost complete and permanent eighth nerve deafness has been reported following use of the drug. Skin eruptions following kanamycin administration have been reported.

Kanamycin is rapidly absorbed after intramuscular injection. Peak blood levels are reached in about 1 hour. Following a single 0.5-gm. dose, levels are within the active range for sensitive organisms for 8 hours and may be potentially active for as long as 12 hours. The drug is excreted in the urine and is virtually completely eliminated in 24 to 48 hours after a single dose. The serum levels are measured to keep the level below 30 mcg./ml. This precaution will prevent serious toxicity.

Kanamycin may be administered orally in 0.5-gm. doses to adults for preoperative bowel sterilization or for the control of some intestinal infections or carrier states.

By exact dosage adjustments, hydration of the patient, and careful management, toxicity can be controlled or prevented. The use of audiograms and renal function tests and avoidance of the sequential use of other ototoxic drugs will prevent the development of untoward effects. Elderly patients are more subject to nephrotoxicity with the drug. Kanamycin, if employed properly, can be a very useful antibiotic in life-threatening gram-negative infections (Foster, 1963).

### Paromomycin

**Paromomycin (Humatin)** is produced by the soil organism designated as *Streptomyces rimosus*. It occurs as a white, amorphous, water-soluble basic antibiotic or the neutral sulfate salt. Its chemical structure has been determined as composed of paramobiosamine, ortho(diaminohexosyl)-D-ribose and paromamine (a glycoside of D-glucosamine) glycosidically linked.

This antibiotic is not absorbed to any appreciable degree from the gastrointestinal tract and is not intended for use in systemic infections. Paromomycin is indicated in bacterial diarrheas, intestinal amebiasis, and preoperative suppression of intestinal flora. Its spectrum of antibacterial activity resembles that of neomycin. Oral administration in animals proved effective in protozoal infections with *Endameba* and *Trichomonas* and against strains of *Escherichia*, *Klebsiella*, *Paracolobactrum*, *Proteus*, *Shigella*, and *Staphylococcus*. Cross-resistance *in vitro* occurs between paromomycin and neomycin and streptomycin.

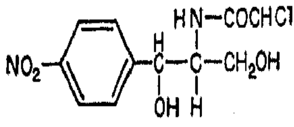
The use of paromomycin in amebiasis is discussed in Chapter 13.

## Chloramphenicol

Chloramphenicol was isolated from a species of streptomyces from Venezuela by Ehrlich *et al.* in 1947. This soil organism is now designated *Streptomyces venezuelae*. The pure antibiotic was soon crystallized, identified chemically, and synthesized. Chloramphenicol was the first antibiotic produced synthetically on a commercial basis.

### Chemistry.

Chloramphenicol is an aromatic nitro compound with the formula D(−)-*threo*-2,2-dichloro-N-[β-hydroxy-α-(hydroxymethyl)-*p*-nitrophenethyl]-acetamide.



Chloramphenicol, U.S.P.

**Chloramphenicol, U.S.P., (Chloromycetin)** occurs as fine white to grayish white, needle-like crystals or elongated plates. It has a bitter taste. Its solutions are neutral to litmus paper. One gram of chloramphenicol is soluble in about 400 ml. of water. It is freely soluble in alcohol. It is reasonably stable in neutral or acid solutions.

**Chloramphenicol Palmitate, U.S.P.** is a white, unctuous, crystalline powder, with a faint odor and a bland, mild taste. It is insoluble in water. The official oral suspension contains 31.2 mg. of chloramphenicol base per ml.

**Chloramphenicol Sodium Succinate** is a light yellow, water-soluble crystalline powder. It is supplied in a readily dissolved "gelsiccated" powder. The solution may be injected intravenously as a 10 per cent solution over a 1-minute period, intramuscularly as a 25 to 40 per cent solution injected deep into the muscle, or subcutaneously as a 10 per cent solution.

### Antibiotic spectrum.

Chloramphenicol is a broad-spectrum antibiotic active *in vivo* and *in vitro* against certain gram-negative and gram-positive bacteria, some rickettsiae and viruses. This antibiotic is active against *Salmonella typhosa* and is the drug of choice in the treatment of typhoid fever. It possesses only a moderate degree of activity *in vitro* against human-type *M. tuberculosis*. Chloramphenicol is effective against *T. pallidum*, although it is not recommended in the clinical treatment of syphilis. Chloramphenicol is not active against yeasts, fungi, or most forms of protozoa. *In vitro* and *in vivo* activity of chloramphenicol against strains of *Aerobacter*, *Escherichia*, *Klebsiella*, *Paracolobactrum*, *Proteus*, *Pseudomonas*, and *Shigella* has been demonstrated. Chloramphenicol in high concentrations inhibits the growth of animal and plant cells.

### Assay.

The antibiotic can be determined by chemical means or by microbiologic assay. There is no unit, and activity is expressed in terms of weight of chloramphenicol. The method of the United States Pharmacopeia for assay for pure chloramphenicol is based upon spectrophotometric absorbancy of a solution at 278 mμ. A microbial assay against *Sarcina lutea* is also required. A chemical assay method was evolved by Glazko *et al.* (1950) for chloramphenicol based upon the reduction of the nitro group to an aromatic amine. This amine is then diazotized and coupled with the Bratton-Marshall reagent to yield a colored compound. This method is not entirely specific because the amount of color formed is proportional to the concentration of other nitro compounds, including certain inactive metabolic products of chloramphenicol.

Clinically, the results from chemical and biologic tests must be evaluated with caution. Samples of blood from patients receiving chloramphenicol give comparable analyses by the two methods for several hours after the drug is first administered. After longer time periods, the chemical tests give higher values than the biologic tests. Apparently chloramphenicol is converted to an inactive form in the body. This inactive form gives a positive chemical test but is not inhibitory to microorganisms. Chemical analytical values for the urine may be 10 times greater than those of the biologic evaluation. As has been pointed out previously, the ultimate value of an antibiotic is not necessarily the concentration of the drug in the blood or tissue but the *anti-bacterial activity resulting in the blood or tissue.*

### Mechanism of action.

In spite of intensive study by numerous workers, the mechanism of action of chloramphenicol remains obscure. The most significant findings have been that chloramphenicol interferes with bacterial protein synthesis. Gale (1951 *et seq.*) and others have shown that chloramphenicol interferes with protein metabolism as indicated by inhibition of glutamate fixation by *S. aureus* and glutamyl polypeptide formation by *B. subtilis*. The synthesis of protein and ribonucleic acid (RNA) is normally closely associated in biologic systems, and it is of interest that chloramphenicol prevents protein synthesis without an effect on RNA synthesis. However, evidence has been found that the RNA which is formed in the presence of the antibiotic is markedly different from that formed in its absence. It is possible that this is the site of inhibition of chloramphenicol on protein syntheses. This action of chloramphenicol may not extend to mammalian cells, although this is speculation (Gale, 1963).

One of the characteristic differences between chloramphenicol and many other antibiotics is the slow development of resistant strains of organisms. For example, full resistance in *E. coli* is developed to streptomycin in a single step, whereas gradual resistance is developed to chloramphenicol. Further, chloramphenicol-resistant strains of a microorganism lose their resistance easily. Rickettsiae do not develop resistance. Clinical experiences indicate that resistance is not a problem in therapy with this antibiotic in typhoid fever or scrub typhus.

Cross-resistance between chloramphenicol and the tetracycline antibiotics has been found in enteric bacteria but not in other species. Chloramphenicol antagonizes the action of antibiotics which act only on growing cells, *e.g.*, penicillin; it has an additive effect with other antibiotics that also inhibit protein synthesis, *e.g.*, tetracyclines and erythromycin. These facts have medical significance in proposed antibiotic combinations for anti-bacterial therapy (Brock, 1961).

### Absorption, distribution, and excretion.

Chloramphenicol is rapidly absorbed when administered orally, as demonstrated by the appearance of high concentrations in body fluids. It is rapidly excreted in man by the kidneys; within 24 hours approximately 90 per cent of an administered oral dose may be accounted for in the urine. After an oral dose of 3 gm., the peak blood serum concentration of approximately 45 μg./ml. is reached in 2 hours; thereafter the amount gradually diminishes until at the end of 10 hours a minimum effective level is attained.

Chloramphenicol is rapidly degraded or inactivated in the body. The major portion of the drug excreted in the urine is in the form of glucuronide compounds. Renal plasma clearance figures indicate that chloramphenicol is largely excreted by glomerular filtration. A glycolic acid amide has been identified in the urine of newborn human infants and adult cats after administration of this antibiotic. Kunin and associates (1959) discovered that microbially active chloramphenicol disappears from the blood of patients with anuria at about the same rate as in subjects with normally functioning kidneys. Metabolic products (glucuronide and arylamine derivatives) are retained in the circulating blood. They concluded that for this antibiotic the loss of anti-bacterial effect was not related to urinary excretion. In spite of the presence of these inactive products, the concentration of unchanged chloramphenicol is high, exceeding 200 μg/ml. after a 1.5-gm. dose orally.

In man, chloramphenicol has been demonstrated in the spinal fluid in a range of 3.8 to 12 μg./ml. within 3 hours after an average dose. To attain this value a blood concentration above 15 μg./ml. should be maintained. Chloramphenicol is transmitted across the human placenta and appears in the fetal circulation. Chloramphenicol is well distributed in the body tissues. It occurs in pleural fluids and is excreted in the bile. Chloramphenicol readily diffuses across the blood-brain barrier regardless of whether or not the meninges are inflamed.

Chloramphenicol palmitate is hydrolyzed in the intestinal tract to free chloramphenicol; therefore, the onset of effective blood levels is slower than after the administration of free chloramphenicol; however, the blood levels persist for longer periods of time. Chloramphenicol sodium succinate is readily hydrolyzed to active chloramphenicol in the tissues and body fluids after parenteral injection.

### Toxicity.

The oral $LD_{50}$ for chloramphenicol for mice has been reported as 245 mg./kg. No toxic effects have been found in animals receiving large oral doses of chloramphenicol for long periods. The chemical structure of the drug, especially the presence of a nitrobenzene group in the molecule, suggests that the antibiotic might be potentially toxic. Nevertheless, the early toxicity studies on animals and man led to the conclusion that chloramphenicol was of very low toxicity.

In 1952, cases of fatal aplastic anemia of an idiosyncratic character and of thrombocytopenic purpura, granulocytopenia, and pancytopenia associated with the administration of chloramphenicol were reported. These untoward hematopoietic phenomena were not found during the first few years of use of chloramphenicol. It is now clear that short or prolonged therapy in susceptible individuals may cause serious blood dyscrasias. Recent evidence has shown that optic neuritis should be added to the serious side effects associated with long-term chloramphenicol therapy. Although these complications are uncommon, they are sufficiently important to warrant the precaution that chloramphenicol should not be used indiscriminately or for minor infections. When prolonged or intermittent administration is required, adequate blood studies must be carried out.

An attempt was made to follow the plasma iron pattern as a single means of detecting erythropoietic depression. By this means, Rubin *et al.* (1958) proposed the early detection of potentially toxic effects of chloramphenicol. However, induced aplastic anemia is still a serious problem that may follow chloramphenicol administration, and therefore judicious use of the drug must be the rule. It should not be used prophylactically, in trivial infections, or in infections in which other less dangerous antibiotics may be used effectively.

In severe, life-threatening infections when chloramphenicol is indicated, adequate doses should be employed. The administration of maximal doses of chloramphenicol (average, 64 gm.) has produced successful therapeutic results without toxicity in patients who could not receive other forms of anti-bacterial drugs (Waisbren *et al.*, 1963).

Chloramphenicol may be particularly toxic for young children, according to some reports (Herrell, 1958). Rubin *et al.* (1958) recorded observations on 5 patients who showed a reduced incorporation of iron into hemoglobin during chloramphenicol administration. However Kunin, Glazko, and Finland (1959) pointed out that associated renal disease in such patients complicates the picture. For these reasons it is generally agreed that for the younger age group the use of chloramphenicol should be restricted to typhoid, salmonellosis and strains of *Staphylococcus aureus* which are resistant to other antibiotics. It should be pointed out that this antibiotic can be administered safely to seriously ill infants and children when necessary.

The most frequently encountered untoward symptoms following oral medication with chloramphenicol are *nausea, gastritis, mild diarrhea,* and *dryness of the mouth* or a *persistent bitter taste in the mouth.*

### Therapeutic use.

Chloramphenicol is effective in a wide range of bacterial, viral, and rickettsial infections, including: urinary tract infections; brucellosis; bacterial and primary atypical pneumonias; staphylococcic and streptococcic infections, especially those resistant to other antibiotics; pertussis; enteric fevers (salmonelloses, including typhoid fever); dysenteries (shigelloses); rickettsial infections (Rocky Mountain spotted fever, typhus fever, scrub typhus fever); acute gonorrhea; granuloma inguinale; and lymphogranuloma venereum.

The infectious diseases in which chloramphenicol is employed are given in table 10-2.

Blood studies of patients receiving chloramphenicol must be made frequently, and the precautions that have been stressed must be observed. It is clear that the drug can be used successfully in therapy when it is indicated if the proper precautions are followed, *e.g.,* routine blood counts, measurement of serum iron, and serial reticulocyte counts. In therapeutic use chloramphenicol continues to be a controversial drug, and reports still appear of large doses administered over long periods of time without toxic effects (Lloyd *et al.*, 1963).

### Dose.

Chloramphenicol is prescribed in 50-, 100-, and 250-mg. capsules for oral administration. An initial dose of 50 to 75 mg./kg. is usually employed. Thereafter, a dose of 250 mg. is given every 2 to 6 hours until the symptoms of the disease have been controlled. A total dose of from 10 to 15 gm. has been found adequate for most acute conditions. The interval between oral doses should not exceed 8 hours in order to prevent the blood level from falling below an effective concentration of about 10 μg./ml. of serum.

Chloramphenicol palmitate in the form of a flavored aqueous suspension is administered orally. The ester is hydrolyzed to free chloramphenicol in the intestinal tract. The dosage on the basis of the parent drug is the same as for chloramphenicol.

Chloramphenicol ophthalmic ointment and

an ophthalmic solution of chloramphenicol are recognized by the U. S. Pharmacopeia.

The adult dose of chloramphenicol succinate is 1 gm. every 6 to 8 hours. This same dose is given either intravenously, intramuscularly, or subcutaneously. A 10 per cent solution is injected intravenously or subcutaneously. For intramuscular injection a 25 to 40 per cent solution is employed.

### THE TETRACYCLINE ANTIBIOTICS

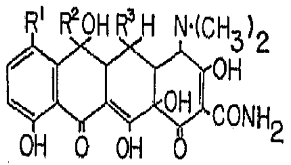
In 1947 in his study of thousands of microscopic fungi among the actinomycetes, Duggar discovered a soil organism for which the name *Streptomyces aureofaciens* was proposed. When grown in culture broth a golden yellow antibiotic was elaborated that was named Aureomycin. In 1950 Finlay and his associates isolated a new actinomycete, *Streptomyces rimosus*, from a soil sample, that produced an antibiotic named Terramycin. In 1952 the unique chemical structures of these two antibiotics were determined, and a third compound was prepared that possessed anti-bacterial properties. As a class, these antibiotics are called the tetracyclines, and one member of the class is named tetracycline.

### Chemistry.

The tetracycline antibiotics can be considered as derived from acetate. Certain structural features of this group of antibiotics has suggested that they are derived from a poly-β-keto acid which is formed from acetate. The presence of oxygen on alternate carbon atoms is the feature which indicates this structural origin. This has been substantiated by using $C^{14}$-labeled acetate as a source of carbon for biosynthesis. The structures of the tetracycline antibiotics are given in table 10-3. Tetracycline is prepared by dechlorinating chlortetracycline by catalytic hydrogenation with palladium. It can also be made by fermentation. Demethylchlortetracycline was made in 1957 by chemical manipulation of tetracycline. Subsequently, it was found in the metabolic products of a mutant strain of *Streptomyces auriofaciens.* Many other tetracycline derivatives have been studied for their anti-bacterial properties. Those possessing therapeutic promise are under investigation. In 1962 the first total synthesis of a tetracycline antibiotic that possessed the full biologic activity of this class of drugs was achieved.

TABLE 10-3

*Structures of the Tetracycline Antibiotics*



| Drug | R¹ | R² | R³ |
|---|---|---|---|
| Tetracycline | H | $CH_3$ | H |
| Chlortetracycline | Cl | $CH_3$ | H |
| Oxytetracycline | H | $CH_3$ | OH |
| Demethylchlortetracycline | Cl | H | H |

Tetracyclines decompose when improperly stored under extreme conditions of heat and humidity, and the resulting products may be toxic (see page 111).

**Tetracycline, U.S.P. (Achromycin, Panmycin, Polycycline, Tetracyn).** Tetracycline Hydrochloride, U.S.P., and Tetracycline, U.S.P., are yellow, odorless, crystalline powders. One gm. of tetracycline base dissolves in 2500 ml. of water; 1 gm. of the hydrochloride dissolves in 10 ml. of water. The potency is reduced in solutions of pH below 2 and in alkali hydroxide solutions.

**Tetracycline Phosphate complex (Panmycin Phosphate, Sumycin, Tetrex).** This form of tetracycline is a stable, yellow, crystalline solid relatively insoluble in water. It is more rapidly and completely absorbed from the gastrointestinal tract than are the free base or the salts.

**Chlortetracycline, N.F. (Aureomycin).** It is a golden yellow crystalline amphoteric substance. It forms a hydrochloride and a sodium salt; the latter is unstable. One gm. of Chlortetracycline Hydrochloride, N.F., is soluble in 75 ml. of water. For clinical use the solution should be freshly prepared.

Chlortetracycline calcium is used for topical application or administered orally as a syrup or drops to patients who cannot take dry forms of the drug.

**Oxytetracycline, N.F. (Terramycin).** This is a yellow, odorless, crystalline amphoteric substance. One gm. of the neutral base dissolves in about 2000 ml. of water. One gm. of the hydrochloride is soluble in 2 ml. of water. Solutions of the base and hydrochloride are not stable at a pH below 2 and are rapidly destroyed by alkali hydroxide solutions.

**Demethylchlortetracycline Hydrochloride (Declomycin Hydrochloride).** This compound is 7-chloro-6-demethyltetracycline. It is prepared chemically from tetracycline or by semi-synthetic methods from a precursor fed to *Streptomyces* *aureofaciens.* The hydrochloride is a yellow, water-soluble, crystalline substance. The molecule is more stable to acid or alkali media and to high temperature than the other tetracyclines.

### Antibiotic spectrum.

While individual clinical experiences with these agents indicate that some possess greater efficacy in certain cases, they are sufficiently similar to be considered as a group. The tetracyclines resemble chloramphenicol in their wide antibiotic spectrum. They are active against a variety of gram-positive and gram-negative microorganisms, many of which are also susceptible to other antibiotics. They are also effective against infections caused by *Rickettsia,* the *virus of lymphogranuloma* and *psittacosis,* and *viral pneumonia.* In addition, they are active against the intestinal forms of the *Endamoeba histolytica.* Infections in which the tetracyclines are effective are set forth in table 10-2.

### Mechanism of action.

Very little is known of the mechanism of action of these antibiotics. Gale (1960) suggested that the tetracyclines may inhibit protein synthesis at growth-inhibitory concentrations in a manner similar to chloramphenicol.

Relatively few modifications can be made in the structure of the tetracyclines without loss of anti-bacterial activity. The high oxygen-nitrogen content of these antibiotics is thought to be responsible for their compatibility with fluids and tissues of living organisms. Oxytetracycline, for example, appears to have positive and negative poles that enable it to form both acidic and basic salts, analogous to amino acids of living cells. The molecule as a whole determines the anti-bacterial properties rather than the presence or orientation of individual groups. The chelating action of these antibiotics with metal ions, removing them from essential enzyme active sites, may account for their effect in inhibiting protein synthesis in bacteria (Gale, 1960).

### Absorption, distribution, and excretion.

Following either oral or parenteral administration, the tetracyclines are readily absorbed. There are significant differences, however, with respect to absorption, excretion, and gastrointestinal side effects. Tetracycline appears to be absorbed better than chlortetracycline, oxytetracycline, or demethylchlortetracycline, and its concentration in the blood is higher and more prolonged than equivalent doses of the other drugs. It is less likely to produce severe gastrointestinal distress. However, after repeated oral doses, demethylchlortetracycline produces blood levels higher than do equal doses of the other tetracyclines.

In the absence of infection tetracycline passes into the cerebrospinal fluid more effectively than the other tetracyclines, but relatively little of these antibiotics passes the blood-brain barrier. These drugs diffuse into lung, spleen, kidney, and liver tissue and are excreted in the bile.

Tetracycline is rapidly excreted in the urine, and, like oxytetracycline and chlortetracycline, doses must be administered every 6 hours. Demethylchlortetracycline has a slower renal excretion and higher stability in the body. It is excreted about half as rapidly as tetracycline (Finland and Garrod, 1960). The tetracyclines persist in the body, and detectable amounts can be found in the urine 2 days after a single oral 0.5-gm. dose. An appreciable amount is excreted in the feces. A total of about 50 per cent is accounted for by excretion; the remainder presumably undergoes destruction in the body. These drugs may possess a teratogenic effect, and some workers recommend that they should not be administered to pregnant women (Cohlan *et al.,* 1963).

### Fluorescence and chelates.

The tetracyclines complex or chelate with physiologically significant ions, *e.g.,* calcium, magnesium, iron, and copper. The plasma protein binding capacity is considerable, from 50 to 75 per cent (Remington and Finland, 1962). Tetracyclines are deposited in the sites of new mineralization of bone and cartilage and can be used as a means of labeling newly formed bone. Fluorescent microscopy reveals the bluish fluorescence of the antibiotic-calcified tissue. The drugs have been identified in teeth, fingernails, and tumors (Frost *et al.,* 1961).

Tetracycline-induced fluorescence of gastric sediment may be of value as a means of detecting gastric cancer and differentiating benign from malignant lesions of the stomach. The antibiotic produces a bright, golden yellow complex with washings from the stomachs of patients with gastric cancer (Berk and Kantor, 1962).

### Therapeutic use.

The broad-spectrum antibiotic tetracyclines have essentially the same general use as chloramphenicol. They are not quantitatively identical antimicrobially. Species and strain variations of the infecting organisms may account for major differences in the degree of susceptibility or resistance to a particular tetracycline. Thus, while the average antistreptococcal activity of 300-mg. doses of demethylchlortetracycline is essentially the same as that of 500-mg. doses of tetracycline, the activity of the former persists much longer in the blood after the last dose (Remington and Finland, 1962). It is generally agreed that the potency *in vitro* of demethylchlortetracycline against most strains of susceptible organisms is equal to or greater than that of the other tetracycline antibiotics. In recent years tetracycline has largely replaced oxytetracycline and chlortetracycline.

The dosage of tetracycline, oxytetracycline, and chlortetracycline is modified depending upon the severity, response, and susceptibility of the specific infection. The average daily adult dose is 1 gm. or more in divided 250-mg. doses orally, every 4 to 6 hours. Children receive from 10 to 40 mg./kg. in proportion to their age and weight. Very large oral doses are not absorbed efficiently.

The usual oral adult dose of demethylchlortetracycline is 600 mg. per day in 2 or 4 divided doses. Single doses exceeding 300 mg. are not administered.

These antibiotics are administered throughout the treatment period and for 24 to 48 hours after fever and other symptoms have subsided. Demethylchlortetracycline is slowly excreted and effective serum concentrations are maintained for 12 to 24 hours after the last dose of the drug.

The tetracycline antibiotics are poorly absorbed from intramuscular injection sites. Intravenously, the drugs are administered in properly buffered solutions, usually on the basis of 20 to 25 mg./kg. of body weight every 24 hours.

The various formulations of the tetracyclines with sodium hexametaphosphate or glucosamine that formerly were reported to give enhanced blood levels are now largely discredited. These dosage forms are comparable in clinical efficacy to the unmodified antibiotics.

### Toxicity.

These antibiotics have a remarkably low systemic toxicity. Animals will tolerate daily doses without experiencing toxic side effects; in fact, some will grow at an increased rate.

Most of the untoward reactions observed following the use of these drugs have been related not to the antibiotics *per se,* but to the change in the intestinal bacterial flora brought about by the presence of the drug in the intestine. *Nausea, vomiting, epigastric distress,* and *diarrhea* are the most common symptoms. A distressing side effect has been *rectal* and *anal pruritis* associated with a burning sensation.

It is now recognized that when these antibiotics are administered orally over extended periods the drugs produce a profound change in the normal bacterial flora of the mouth, vagina, and intestine. There is an overgrowth of yeast-like organisms that normally are held in check by the resident bacterial flora. The microorganism frequently identified is the monilia, *Candida albicans.* It is believed that this proliferation accounts for the numerous symptoms of gastrointestinal distress, glossitis, stomatitis, and proctitis associated with broad-spectrum antibiotic therapy.

Skin lesions have been reported following the use of the tetracyclines. Contact dermatitis is rare and moniliasis may be suspected. Moniliasis of the lungs has followed the prolonged use of tetracyclines for the treatment of bronchiectasis.

Demethylchlortetracycline has produced a curious photodynamic reaction in some subjects who took the drug and exposed themselves to bright sunlight. An exaggerated sunburn with high fever, eosinophilia, and increased blood platelets characterizes the reaction. This appears to be a true phototoxicity and not a hypersensitivity phenomenon, although anaphylactoid reactions have been reported. Both reactions are rare.

The decomposition products of the tetracyclines have been reported to produce an acute syndrome of vomiting, proteinuria, glycosuria, acidosis, and aminoaciduria. The degradation products, epianhydrotetracycline and anhydrotetracycline, have been shown to be the cause (Frimpter *et al.,* 1963). The use of lactose in the capsules as a filler for chlortetracycline prevents the decomposition of this antibiotic. It is surprising that in the 10 years that these drugs have been used these serious side effects were not discovered sooner. The toxicity develops rapidly, within 2 to 3 days after administration of the deteriorated drug, even when there is only partial decomposition of the antibiotic.

The evidence is now at hand that the tetracyclines are quickly and rather permanently deposited in bone and deciduous teeth and nails after therapeutic doses. In addition, these doses can interfere with the growth and development of bones and teeth of infants (Cohlan *et al.*, 1963). Their teratogenic properties are essentially unknown. For these reasons, tetracyclines should not be given to pregnant women or infants unless no other drug can control the infection. With the host of antibiotic drugs available, this is not likely to be a problem for the clinician.

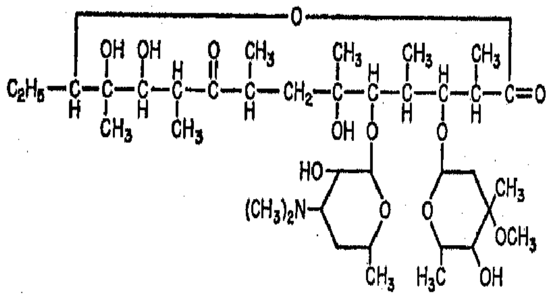
## THE MACROLIDE ANTIBIOTICS

The macrocyclic lactone or macrolide antibiotics are large molecular weight compounds with long chain aliphatic acid lactone rings linked glycosidically to novel sugars. Some antibiotics of this group contain dimethylamino sugars; others are without an amino group and contain no nitrogen. Erythromycin, oleandomycin, and carbomycin (magnamycin) have found therapeutic uses. Several other members of the class have been isolated and characterized structurally (Miller, 1961).

The macrolide antibiotics are elaborated by the *Actinomycetales*, particularly by the genus *Streptomyces*.

### Erythromycin.

**Erythromycin, U.S.P. (Ilotycin, Erythrocin).** This is an antibiotic elaborated by a strain of *Streptomyces erythreus* isolated from a soil sample collected in the Philippines (Clark, 1953). Erythromycin base is a white, crystalline basic compound. One gm. of the base dissolves in about 1000 ml. of water. The salts formed by mineral acids are unstable, but the glucoheptonate and lactinobionate salts are sufficiently stable and water-soluble for intravenous or intramuscular injection.



Erythromycin, U.S.P.

**Erythromycin Tablets, U.S.P.** contain 0.1 or 0.25 gm. of erythromycin base. The ophthalmic ointment contains 5 mg./gm.; the topical ointment is 1 per cent.

**Erythromycin estolate (Ilosone)** is erythromycin propionate lauryl sulfate. This is the lauryl sulfate salt of the propionic acid ester of erythromycin. This preparation is acid-stable and will produce therapeutic blood levels when administered orally. It is administered as 0.125- or 0.25-gm. capsules, as drops, 0.1 gm. per ml., or as oral suspension, 0.25 gm./ml.

**Erythromycin Ethylcarbonate, U.S.P.** is a salt suitable for extemporaneous preparation of flavored suspensions of the drug for oral use.

**Erythromycin Stearate, U.S.P.** is administered orally as buffered tablets of 0.1 or 0.25 gm. The blood levels obtained with this salt are comparable to those achieved with erythromycin base.

**Erythromycin Glucoheptonate, U.S.P.** may be injected intravenously. The solution is prepared by dissolving the equivalent of 0.25 gm. of erythromycin base in 10 ml. of water for injection. Other diluents should not be used because they interfere with the solubility of the antibiotic salt. The initial solution is diluted to 250 or 500 ml. with isotonic sodium chloride or 5 per cent dextrose solution and administered intravenously for 20 to 60 minutes. The dose may be repeated every 6 hours.

**Erythromycin Lactobionate, U.S.P.** is administered either intravenously or intramuscularly. Dosage is expressed in terms of the base. The dose is 1 to 2 mg. per pound of body weight injected at 8- to 12-hour intervals. The same precautions are observed in preparing the solution as with erythromycin glucoheptonate.

**Anti-bacterial properties.** Erythromycin has a penicillin-like anti-bacterial spectrum. It is active *in vitro* and *in vivo* against several types of microorganisms that are not sensitive to penicillin. Most of the gram-positive bacilli, certain gram-negative varieties such as *Neisseria*, *Hemophilus*, *Brucella*, *Pasteurella*, and the spirochetes *Treponema pallidum* and *Leptospira icterohemorrhagiae* are sensitive to erythromycin.

The range of activity of erythromycin includes the *Endameba histolytica*, trypanosomes and rickettsiae. Bacteria of the colon-typhoid group, mycobacteria of tuberculosis, enterococci, the fungi and the pleuropneumoniae-like organisms are nonsensitive to erythromycin.

Like penicillin, erythromycin is bactericidal in low concentration for rapidly multiplying hemolytic streptococci or staphylococci. It may be only weakly bacteriostatic for mature cultures, depending upon the sensitivity of the microorganism. By repeated subcultures of erythromycin-sensitive bacteria it is possible to obtain strains exhibiting a resistance to this antibiotic. Resistant strains of staphylococci and streptococci have been encountered clinically after erythromycin therapy.

**Absorption, distribution, and excretion.** Erythromycin is well absorbed from the gastrointestinal tract, although it is partially destroyed by gastric secretions. After absorption erythromycin is distributed to body tissues and fluids, including amniotic fluid, saliva, bile, aqueous humor, milk, and, to a lesser degree, the spinal fluid. The antibiotic does not readily traverse the blood-brain barrier.

High tissue concentrations are attained after oral administration; the highest are found in the liver and the bile, the lowest in brain tissue. After intravenous administration of erythromycin glucoheptonate to dogs, ⅓ of the dose was excreted in the bile and 16 per cent in the urine. The esters of erythromycin are hydrolyzed, and the antibiotic appears in the blood as erythromycin free base and ester.

Clinically, the oral administration of a suitable dosage form of erythromycin will provide effective serum concentrations over a period of 6 hours or longer. The peak blood level will depend upon the form in which the drug is administered but usually is found 1 to 2 hours after the oral dose.

**Toxicity.** Tests on animals have indicated that the acute toxicity of this antibiotic is very low. When used clinically, erythromycin may produce gastrointestinal disturbances, including nausea, vomiting, diarrhea, and prostration. These side effects are not frequent and seem to be related to dosage; smaller doses rarely cause intestinal irritation. Unlike the broad-spectrum antibiotics, erythromycin rarely induces a significant change in the intestinal flora. With prolonged therapy for more than 2 weeks, repeated blood cell counts are desirable.

**Therapeutic use.** Erythromycin is valuable primarily because it is active against staphylococci resistant to the penicillins and the tetracyclines. At one time it was employed to control the spread of penicillin-resistant staphylococcal infections in hospitals. It is effective in acute and chronic intestinal amebiasis. It is equally effective as silver nitrate when applied as an ophthalmic ointment prophylactically against ophthalmia neonatorum. Erythromycin has been compared to oleandomycin in treating infections caused by gram-positive organisms. While both drugs are effective, they should not be considered as anti-bacterial equivalents. Erythromycin is not employed against nonhemolytic streptococci or meningococci and gonococci except under rare circumstances.

Resistance to erythromycin has been observed chiefly in chronic staphylococcal or streptococcal infections. There may be a rapid increase in erythromycin-resistant staphylococci in patients and hospital personnel during the intensive use of this agent in hospitals. The high incidence of erythromycin-resistant staphylococci encountered in hospitals in the past few years has decreased the usefulness of this antibiotic.

### Oleandomycin.

Oleandomycin belongs to the macrolide group of antibiotics. It is a basic antibiotic elaborated by a strain of *Streptomyces antibioticus*. Its precise chemical structure is not known. The molecular formula is $C_{35}H_{61}O_{12}N$. On hydrolysis the dimethylamino sugar desosamine and the neutral sugar oleandrose are formed. The phosphate salt is suitable for oral, intravenous, or intramuscular injection. The triacetyl ester is given by mouth.

**Oleandomycin Phosphate, N.F. (Matromycin)** is used in infections in a manner similar to erythromycin. The phosphate salt is a colorless, crystalline powder, freely soluble in water. It exhibits antimicrobial activity *in vitro* against staphylococci, streptococci, pneumococci, and a number of other gram-positive organisms. It is effective against some gram-negative organisms, rickettsiae, large viruses, and protozoa. It has negligible activity against coliform bacteria and other organisms of the coliform group.

Clinical experiences with oleandomycin have demonstrated that it is useful in infections caused by staphylococci, including strains naturally resistant to erythromycin and penicillin, and strains that have emerged as resistant variants from the continued use of these and other antibiotics. It is useful in treating $\beta$-hemolytic streptococcal and pneumococcal infections, although the tetracyclines may be the drugs of choice. The evidence for the use of oleandomycin in meningococcal and *H. influenzae* infections is equivocal. The antibiotic is effective in gonorrheal infections. Most authors stress the use of this antibiotic against infections caused by organisms resistant to other antibiotics. For this reason its indiscriminate use is to be discouraged, for cross-resistance between erythromycin, other antibiotics, and oleandomycin is known. Prolonged therapy with oleandomycin can produce resistant strains of staphylococci.

Oleandomycin phosphate is given in oral doses of 250 to 500 mg., 4 times daily for adults. A dose of 50 to 100 mg. per kg. of body weight every 24 hours is administered by intravenous injection in equally divided amounts. It is rarely given by intramuscular injection.

**Triacetyloleandomycin, N.F.** (**Tao, Cyclamycin**) is administered orally. The triacetyl ester is a colorless, crystalline powder only slightly soluble in water. This form of the antibiotic is more rapidly and completely absorbed than the phosphate salt; the dose is the same. Upon oral ingestion, deacetylation may give rise to as many as 6 biologically active intermediates, each with different solubilities, biologic activities, and blood absorption characteristics. The prompt blood levels are related to the absorption characteristics of these intermediates. Glucosamine has been combined with this antibiotic form to enhance further the absorption of the drug from the gastrointestinal tract.

The claims made that triacetyloleandomycin produces higher blood levels than oleandomycin or erythromycin, must be evaluated in terms of antibacterial activity. There is evidence that there is no significant difference on the basis of bacterial growth inhibition. Erythromycin appears to be a superior antibiotic.

The toxicity of oleandomycin for experimental animals is low, and hematologic and biochemical findings have not indicated untoward effects. Side effects that have been reported during therapy were mild diarrhea and occasional cutaneous hypersensitivity reactions. As with other antibiotics, the possibility of overgrowth of yeast-like organisms must be considered, although the risk is less likely with oleandomycin than when other broad-spectrum antibiotics are used.

There have been reports of abnormal liver function tests following the administration of triacetyloleandomycin in doses of 1 gm. per day for 14 days or longer. Jaundice has been observed infrequently. The antibiotic is not intended for prophylactic use, and there is no need to employ the drug for prolonged therapy. Accurate bacteriologic identification of the infecting organisms and susceptibility tests indicating the use of oleandomycin would probably prevent untoward hepatic toxicity.

## Unclassified Antibiotics

### Vancomycin (Vancocin).

Vancomycin is an antibiotic produced by strains of *Streptomyces orientalis*, isolated in 1956 from soil samples collected in Indonesia and India. Its structure has not been determined. The hydrochloride salt is a white solid, very soluble in water. Its molecular weight is about 3300.

Laboratory and clinical trials with vancomycin indicate that it is bactericidal and primarily active against gram-positive bacteria, particularly micrococci. It does not display cross-resistance to other antibiotics, it has a relatively low toxicity, and acquired staphylococcal resistance to vancomycin has not been reported to date. For these reasons vancomycin may be the antibiotic of choice in the treatment of infections caused by bacteria that cannot be inhibited or killed by other antibiotics. A typical use of vancomycin is in the treatment of staphylococcal infections resistant to other antibiotics.

Vancomycin may be administered intravenously in the treatment of penicillin-resistant strains of α-nonhemolytic streptococci. It is not desirable to use this antibiotic in β-hemolytic streptococci or pneumococci infections that normally are sensitive to penicillin therapy. It may be selectively effective in acute bacterial endocarditis when the causative organism is penicillin-resistant. In gram-positive enterococcal infections, vancomycin may be combined with erythromycin or a tetracycline. After intravenous injection the drug is excreted in the urine. High concentrations of the antibiotic appear in the urine even after a single 0.5-gm. dose, and significant amounts (about 100 mcg. per ml.) are found after 24 hours. The drug is not metabolized to a great extent in the body. Impaired renal function is a contraindication for vancomycin therapy.

Toxic effects produced by vancomycin include occasional dermatitis and chill or localized phlebitis after intravenous injections. After prolonged therapy an impairment of hearing may develop. Large doses of vancomycin, or its administration to patients with renal damage, may produce ototoxic effects. Blood urea nitrogen determinations are indicated for patients receiving intensive therapy or treatment for prolonged time periods. Apparently, hypersensitivity reactions can occur after vancomycin injection; a non-fatal anaphylactic reaction has been reported.

The usual adult intravenous dose of vancomycin hydrochloride is 2 gm. daily. A dose of 500 mg. is injected every 6 hours. A solution of vancomycin hydrochloride containing 500 mg. per 10 ml. is injected intravenously over a 4- to 5-minute period. A more dilute solution containing this dose in 100 to 200 ml. of isotonic sodium chloride or 5 per cent dextrose, administered over a 30-minute period, is most satisfactory. Vancomycin should be reserved for critically ill patients with deadly infections of strains of staphylococci that are resistant to the other antibiotics. Bacterial susceptibility tests are essential before prescribing this antibiotic.

### Ristocetin (Spontin).

This antibiotic is produced by a species of actinomycetes named *Nocardia lurida*, isolated in 1957 from a soil sample collected in Colorado's Garden of the Gods. Its chemical structure is not known, but two components, ristocetin A and B, have been identified. The drug preparation is a lyophilized mixture of these two ristocetins.

The antibiotic is bactericidal for gram-positive bacteria. It has been used in treating staphylococcic pneumonia, subacute bacterial endocarditis identified as staphylococcic or enterococcic in character, septicemia, abscesses, and osteomyelitis. Ristocetin is active *in vitro* against *M. tuberculosis*, but it is not recommended for use in tuberculosis at the present time.

The chief role of ristocetin appears to be in the treatment of infections caused by staphylococci or enterococci that are known to be resistant to other antibiotics. Because accurate bacteriologic identification of the sensitivity of the invading strain of staphylococci must be made prior to ristocetin therapy, the degree of sensitivity of the organism to the commonly used antibiotics should be simultaneously determined. In some cases ristocetin may be life-saving if the organism is not sensitive to other drugs.

Ristocetin is administered intravenously because it is not adequately absorbed by mouth. Intramuscular injections are irritating. For these reasons oral antibiotics such as the tetracyclines and penicillin are preferred if the infecting organism is not a resistant strain. Staphylococci and other pathogenic microorganisms apparently do not develop resistance to ristocetin. This fact may be related to the bactericidal action of the drug.

The usual intravenous daily dose is 25 to 50 mg./kg., but higher doses may be used in endocarditis. The total daily dose is injected at intervals of 8 to 12 hours in 2 or 3 portions. Ristocetin is usually administered to hospitalized patients; therefore, the drug is best given by intravenous drip technic. The solution is prepared by dissolving the dry, sterile, lyophilized powder in a sufficient 5 per cent dextrose solution to make a 0.2 per cent solution of the drug. Concentrations higher than 1.25 per cent cannot be tolerated. The desired dose of the drug is administered over a 30- to 45-minute period.

Side effects associated with ristocetin therapy are related to irritation of the intima of veins and thrombophlebitis. These effects are more marked following the use of more concentrated solutions. Skin eruptions, diarrhea, and fever have been reported in a few patients after several days of therapy. Renal toxic effects have not been reported, and anaphylactic reactions have not been caused by the drug. Because side effects are most frequent in patients receiving the larger doses, it is recommended that the adult dose should not normally exceed 2 gm. per day.

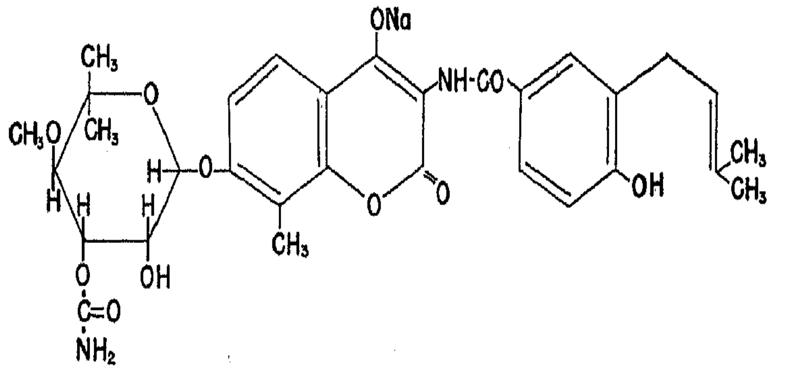
Serious hematologic changes may be caused by ristocetin. Leukopenia with neutropenia, acute anemia, and platelet depression has been reported. Thrombocytopenia has been found, but not agranulocytosis or abnormal bone marrow changes. Toxic effects on the eighth cranial nerve have also been reported to occur occasionally.

### Novobiocin, U.S.P. (Albamycin, Cathomycin).

Novobiocin produced by *Streptomyces niveus*, *S. griseus*, or *S. spheroides* was first reported in 1956. This antibiotic forms both acid and neutral salts. Its structure has been determined. Novobiocin calcium and sodium are white crystalline powders. The calcium salt is soluble 1:250; the sodium salt is very soluble in water. It can be considered to be composed of a sugar, noviose, a substituted coumarin, and a substituted benzoic acid.

Novobiocin free base is not absorbed from the gastrointestinal tract. The calcium salt is stable in aqueous suspension and is suitable for oral administration, as is the more soluble sodium salt. The discussion which follows refers to the sodium or calcium salts. Adequate blood levels are reached within 2 to 3 hours and are maintained for at least 8 hours. The antibiotic diffuses into ascitic and pleural fluid but not into the cerebrospinal fluid unless the meninges are inflamed. It is concentrated in the liver and excreted in the bile and feces. Urinary excretion accounts for about 3 per cent of the dose.

The anti-bacterial spectrum of novobiocin is limited; it inhibits many gram-positive organisms but has little or no activity against most gram-



Novobiocin Sodium, U.S.P.

negative bacilli of the enteric group. It is about as effective as erythromycin against staphylococci that are antibiotic-resistant and it does not exhibit cross-resistance. It is effective against some strains of *Proteus vulgaris* and coliform bacteria.

Most writers stress the importance of reserving the use of novobiocin for those infections caused by resistant strains of organisms resulting from the use of other antibiotics. It is well to point out that strains resistant to novobiocin may develop. There is some evidence that novobiocin is most effective when used jointly with another antibiotic, especially erythromycin, when a prolonged period of treatment is anticipated. An example would be suppurating staphylococcal abscesses.

The usual adult oral dose of either salt is 500 mg. every 6 to 8 hours for infections of moderate severity and 250 mg. every 6 to 12 hours for milder infections. It may be administered intravenously or intramuscularly as the sodium salt.

Allergic dermatitis may occur in about 8 per cent of patients receiving novobiocin. Anemia, leukopenia, and pancytopenia have followed the use of the drug, and it is a wise precaution to make frequent blood examinations during therapy. Mild gastrointestinal symptoms of abdominal cramping, nausea, and an increased number of liquid stools have been reported by patients taking the drug. A metabolite of the drug produces a yellow, serum bilirubin-like pigment which causes yellowing of the sclerae and false bilirubin values. In the presence of liver damage the antibiotic should be used with care.

When this antibiotic is used, therapy should be intense and designed to clear the infection promptly before resistant strains of the bacteria can develop. The drug should not be used for minor infections.

### Antibiotics Applied Topically

There are several useful antibiotics that are not absorbed to a significant degree when taken orally, apparently because of the complex nature of their large molecules. Most of these drugs are toxic if employed parenterally, but in certain instances they may be used effectively in various ways in treating infections caused by microorganisms that are not susceptible to any other anti-bacterial agent. The treatment of acute infectious gastroenteritis, especially in infants, by orally administered, nonabsorbable antibiotics such as polymyxin B or neomycin illustrates how these drugs can be utilized. In general, the antibiotics considered in this section are used topically. When employed in this manner, these drugs are not likely to encourage the emergence of resistant strains of organisms. There are special dosage considerations for each of these antibiotics; they differ chemically, therapeutically, and toxicologically.

### Tyrothricin.

Dubos in 1939 succeeded in isolating, from an extract of cultures of the soil, bacillus *B. brevis*, an antibiotic which he named *tyrothricin*. Dubos selected this name in recognition of Pasteur's first assistant Duclaix, who had studied the bacterial antagonisms of the *tyrothrix bacteria* in cheese manufacture. Chronologically, tyrothricin antedated penicillin in antibiotic therapy. It was not destined to play as prominent a role in therapy, however, because of its toxicity.

Tyrothricin is employed medicinally as an alcohol-soluble, water-insoluble material derived from autolyzed cultures of sporulating *B. brevis*. Its anti-bacterial activity is caused by two compounds, *gramicidin* and *tyrocidine*. Tyrothricin contains about 20 per cent gramicidin and about 80 per cent tyrocidine. These are crystalline, neutral, cyclic polypeptides with high molecular weights.

The anti-bacterial activity of these two substances is markedly different. Tyrocidine behaves as a disinfectant; it inhibits cell respiration and disrupts the cell walls of bacteria. Gramicidin inhibits growth but does not lyse bacteria; it stimulates the oxygen consumption of nongrowing cells. Gramicidin is the more active of the two, especially against gram-positive organisms. Tyrocidine, while present to the greater extent in tyrothricin, possesses only a limited degree of activity against gram-negative forms. It has little or no activity against most gram-positive bacteria except in very high concentrations. On the other hand, gramicidin in very minute amounts exerts a marked anti-bacterial effect on many of these organisms. It is therefore largely responsible for the activity of tyrothricin. For clinical use, the antibiotic substances present in tyrothricin are not separated.

**Tyrothricin, N.F. (Soluthricin.)** Tyrothricin occurs as a white, grayish white, or brownish white powder. It is odorless and almost tasteless.

**Toxicity.** Tyrothricin is highly hemolytic *in vivo* and *in vitro*. For this reason it cannot be safely administered orally or by parenteral injection. The hemolytic activity is primarily due to tyrocidine, although gramicidin will cause a delayed hemolysis.

Local application on surfaces such as wounds and ulcers does not produce systemic toxic symptoms. Bleeding has been reported following the application of an alcoholic solution of the drug to a fresh wound. Reports of both parosmia and anosmia have been made, indicating that its use topically in nose drops is not without hazard. Tyrothricin may cause irritative meningitis following its use for irrigation of cavities near the subarachnoid space.

**Therapeutic use.** This antibiotic must be restricted to topical application. It is effective against gram-positive pneumococci, streptococci, and staphylococci. Tyrothricin has been found useful in the treatment of superficial indolent ulcers, abscesses of the skin and soft tissues, mastoiditis, empyema, acute sinusitis, osteomyelitis, and certain types of ophthalmic infections. The drug is commonly employed as an isotonic solution containing 0.5 mg. per ml. by instillation, irrigation, or wet dressing. The presence of body fluids do not greatly inhibit the activity of tyrothricin; however, the exudates from gram-negative infections may be strongly inhibiting. High concentrations produce local irritation and pain at the site of application. Clinically, tyrothricin is supplied for topical application as a 2.5 per cent concentrate in alcoholic solution, requiring dilution with sterile distilled water for therapeutic use. Because of its water insolubility a cloudy suspension results. The suspension should be freshly prepared.

### Bacitracin.

The bacitracins are a group of complex polypeptides produced by a gram-positive, sporulating bacillus, *B. subtilis*. The structure of bacitracin A, the form which exhibits the anti-bacterial effects, is known.

**Bacitracin, U.S.P. (Baciguent)** is a hygroscopic powder, pale buff in color. It is freely soluble in water. The solution deteriorates rapidly in anti-bacterial potency at room temperature.

Bacitracin resembles penicillin in its activity toward a variety of gram-positive bacteria and spirochetes. It fails to inhibit most gram-negative species. It is assayed on the basis of its anti-bacterial potency against a standard strain of *Micrococcus flavus*. The United States Pharmacopeia requires a potency of not less than 40 units per mg., except when intended for parenteral use; a potency of 50 units per mg. is then required.

**Toxicity.** Like other bacterial polypeptides, bacitracin produces kidney damage if injected parenterally. Its nephrotoxicity limits its clinical usefulness. After its use in systemic infections, the increase in blood urea nitrogen and abnormal urinary changes associated with potential kidney damage are its most serious toxic effects.

**Absorption and excretion.** Bacitracin is absorbed following intramuscular injection and excreted in the urine. It is poorly absorbed from the gastrointestinal tract, and oral doses do not give measurable blood concentrations.

**Therapeutic use.** Bacitracin has been most useful when applied locally for the management of surgical infections, furuncles, abscesses, and numerous pyogenic skin infections caused by sensitive gram-positive bacteria.

Bacitracin may be indicated when bacterial sensitivity tests show that a favorable response is to be expected and when the organism is resistant to less toxic antibiotics. The recommended dose ranges between 10,000 and 20,000 units, given intramuscularly at 6-hour intervals. It is imperative that renal function be carefully observed and that fluid intake and urinary output be measured daily.

In neurosurgical infections, bacitracin may be injected intrathecally or intraventrically. It may be used topically and as an irrigation for wet dressings in the peritoneal cavity, and in contaminated intestinal surgery. Bacitracin has been used in the treatment of intestinal amebiasis. An aerosol mist of a bacitracin solution has been employed safely in pulmonary diseases.

Bacitracin is active against a wide variety of microorganisms, and the fact that relatively small amounts of the antibiotic may act synergistically with other antibiotics makes this drug potentially very useful. In general, organisms do not readily develop resistance to bacitracin *in vivo*, and no enzyme has been found that inactivates the antibiotic. For these reasons a large number of antibiotic combinations have been marketed. Bacitracin is available in combination with neomycin, polymyxin, and tyrothricin. Ointments, tablets, troches, and nasal solutions intended for topical or local application are available. Bacitracin Ointment, U.S.P., contains 500 units per gm. in a petrolatum base.

### Polymyxin.

Polymyxin is a generic name for a number of antibiotics isolated in 1947 from different strains of the soil bacillus, *Bacillus polymyxa.* The various individual antibiotics are designated as polymyxin A, B, C, D, and E. They are basic polypeptides, the salts of which are water-soluble, and they are most active against gram-negative bacteria.

As a group the polymyxins differ one from another in their amino acid content. The polymyxins possess high potency, and are especially effective in infections of *Pseudomonas aeruginosa.* In view of the unusual resistance of this organism to most chemotherapeutic agents, its susceptibility to an antibiotic is of clinical importance. Polymyxin B has been most extensively employed clinically and is the least toxic member of this group of antibiotics. It is composed of the rare $\alpha,\gamma$-diaminobutyric acid, with 6-methyloctanoic acid and the amino acids phenylalanine, leucine, and threonine.

**Polymyxin B Sulfate, U.S.P. (Aerosporin Sulfate).** The U.S.P. requires that this antibiotic exhibit a potency of not less than 6000 units per mg. The antibiotic is assayed against a standard strain of *Brucella bronchiseptica.* It is a white or buff powder freely soluble in water. Its solutions are slightly acid, pH 5, or neutral. Polymyxin B Sulfate Tablets, U.S.P., are intended for oral use in the treatment of gastrointestinal infections that are susceptible to this antibiotic, especially *Shigella* and *Pseudomonas* infections.

**Therapeutic use.** This antibiotic has been used in the local treatment of infections caused by gram-negative bacilli, especially *P. aeruginosa,* by topical application. The dry sterile powder or solutions of 0.1 per cent (10,000 units per ml.) to 0.25 per cent (25,000 units per ml.) are effective and not irritating. Higher concentrations may be irritating. An ophthalmic ointment containing 20,000 units per gm. is available. Adult oral doses of 75 to 100 mg. 4 times daily have been used for nonsystemic treatment of intestinal infections of *Shigella* or *Pseudomonas.* The use of fluorescent antibody technic has made possible the rapid identification of enteropathogenic *E. coli* in the stool. In acute infectious gastroenteritis, the rapid identification of the infecting organisms and their susceptibility to antibiotics has improved the therapy of the bacterial diarrheas. Polymyxin B is a useful antibiotic in these infections.

The toxic reactions, consisting of albuminuria, elevated nonprotein nitrogen blood levels, and depressed renal function, have been sufficiently severe to preclude extensive use of this antibiotic. In certain serious infections of gram-negative organisms not responding to other treatment, polymyxin B sulfate has been used intramuscularly or intrathecally. Serious toxic effects involving the central nervous system with ataxia, weakness, dizziness, and paresthesia have been reported. It is apparent that polymyxin B sulfate is best reserved for those infections that do not respond to other antibiotics.

A significant number of reports in the clinical literature stress the value of polymyxin B sulfate in the treatment of *Pseudomonas* infections in infants and children, postoperative endocarditis caused by *P. aeruginosa,* and persisting pathogenic *E. coli.* In many of these cases relatively large doses of the antibiotic were administered for long periods of time. Toxic effects were not encountered and renal damage did not result from the use of the drug. It appears that for patients with adequate renal function, the nephrotoxic potential need not preclude the use of polymyxin B when it is indicated (Jawetz, 1961).

### THE COLISTINS

Colistin is a polypeptide antibiotic elaborated by the soil bacterium *Bacillus colistinus* (*polymyxa* var. *colistinus*). The exact molecular structure has not been determined, but it has a molecular weight of 969 and is composed of a series of amino and fatty acids. It is closely related chemically and anti-bacterially to polymyxin B. The clinical indications for the colistins are the same as those for polymyxin B. However, the colistins are generally believed to be preferable because of their greater potency and lower toxicity. There is some evidence that colistin is identical with polymyxin E.

### Colistin Sulfate (Coly-Mycin Pediatric Oral Suspension).

Colistin sulfate is a colorless, crystalline, water-soluble salt. It is rapidly bactericidal *in vitro* to gram-negative bacilli (*Pseudomonas, Escherichia, Aerobacter,* and *Klebsiella* species,) but it is not effective against most species of *Proteus* or gram-positive organisms. It is considered to be the best drug for oral use in children in the treatment of diarrhea caused by these susceptible organisms.

Colistin sulfate can cause renal and neural toxicity. Relatively little absorption of the antibiotic takes place from the gastrointestinal tract, except perhaps in infants. For this reason, toxicity reports have been few. The drug has the same potential toxicity as colistimethate sodium.

Colistin sulfate is administered orally to infants and children in 3 divided doses of 3 to 5 mg. of the base/kg. daily. The dosage form contains 5 mg. per ml. of colistin.

### Colistimethate sodium (Coly-Mycin Injectable).

Colistimethate sodium is a white, amorphous compound. It is the sodium salt of the methanesulfonate of colistin. It is an intramuscular dosage form of the drug.

Colistimethate sodium is employed in the treatment of infections of *P. aeruginosa* of the urinary tract, the meninges, and peritoneum. It is indicated in those infections where colistin sulfate would be useful. Colistimethate sodium is less toxic than polymyxin B sulfate and appears to be superior in therapy of infections caused by *Pseudomonas* species.

The most serious toxic effect of colistin is impairment of renal function. A rise in blood urea nitrogen is commonly observed, and serious azotemia has followed the administration of large doses to patients with kidney damage. Circumoral or lingual paresthesias, pruritus, or tingling sensations of the extremities may be produced. Ataxia, visual or speech disturbances, dizziness, and nystagmus have been reported after dosage with the drug. Allergic reactions may be elicited, and cross-sensitivity to polymyxin B may exist. Careful and close attention to the patient is indicated when this antibiotic is administered (Petersdorf and Plorde, 1963).

Colistimethate sodium is injected intramuscularly in doses of 2.5 mg. of the base/kg. daily. A maximal dose of 5 mg./kg. must not be exceeded.

### Neomycin.

Waksman and Lechevalier in 1949 described an antibiotic produced by an actinomyces, *Streptomyces fradiae.* They named this agent neomycin.

Neomycin is a thermostable, water-soluble, basic compound. It forms salts with mineral acids. Neomycin is a mixture of at least three closely related chemical substances, which are designated neomycin A, B, and C. Commercial neomycin contains more than 90 per cent neomycin B. The structure of neomycin B has been determined; it is isomeric with neomycin C. The chemistry of the neomycins has been reviewed by Rinehart (1964).

**Neomycin Sulfate, U.S.P. (Mycifradin, Myciguent).** This antibiotic is assayed by a microbial method against a standard strain of *Micrococcus pyogenes,* var. *aureus.* It contains an amount of neomycin sulfate equivalent to not less than 60 per cent of neomycin base. Neomycin sulfate is a white to slightly yellow powder or fine crystalline mass. It is odorless and hygroscopic. One gram of neomycin sulfate dissolves in about 1 ml. of water.

Neomycin is active *in vitro* against a wide variety of gram-positive and gram-negative organisms, including *Corynebacteria, Neisseria, Aerobacter* and *Escherichia.* It is the most effective antibiotic against *Proteus vulgaris,* according to some authorities.

Neomycin is nephrotoxic and has produced severe impairment of hearing. Although active against the *M. tuberculosis,* this antibiotic is not safe enough to justify its use in man in the treatment of tuberculosis. Orally it is not appreciably absorbed, and neomycin has been used as an intestinal antiseptic and adjuvant to abdominal surgery.

Neomycin should only be used systemically when safer antibiotics are not effective. In serious systemic infections of *K. pneumoniae*, *P. vulgaris*, *P. aeruginosa*, *H. influenzae*, and some gram-negative urinary tract infections that do not respond to other drugs, neomycin may be administered intramuscularly. A total daily dose of 1 gm. administered in 4 separate injections should not be exceeded, and the course of treatment should be limited as much as possible. Resistant strains do not develop, but serious renal or ototoxic effects may result from prolonged use. When neomycin is employed by intramuscular injection for hospitalized patients in the treatment of serious systemic infections, special precautions must be observed to prevent nephrotoxicity and injury to the auditory function of the eighth nerve.

Neomycin solutions are nonirritating to mucous membranes and epithelium. Neomycin is not absorbed from the skin. Neomycin sulfate Ointment, U.S.P., and various combinations of neomycin sulfate with other antibiotics in ointments and topical dosage forms are available. Neomycin is incorporated in many commercial deodorant preparations. Its anti-bacterial effect is presumed to be responsible for decreasing the skin bacterial flora that cause some forms of body odor. Neomycin Sulfate Tablets, U.S.P., are intended for oral use. The suggested dose is 100 mg./kg. divided into 6 equal portions and given orally every 4 hours for intestinal sterilization.

### ANTIFUNGAL ANTIBIOTICS

Numerous antibiotics have been isolated that are active against deep-seated and superficial mycotic injections. Most of these agents are too toxic to be employed for systemic therapy. However, several antibiotics of this class have been proved to be remarkably effective in treating these notoriously refractory infections. Griseofulvin is outstanding in its effectiveness in clearing fungus infections of the skin, amphotericin B is useful against some yeasts and fungi, and nystatin is used in controlling infections caused by monilial organisms.

## Nystatin, U.S.P. (Mycostatin).

Hazen and Brown in 1950 extracted an antibiotic from a soil species, *Streptomyces nouresi*, that possessed activity against the fungi *Candida albicans* and *C. neoformans*. They named this agent fungicidin; later it was named nystatin.

Nystatin is a pale yellow, water-insoluble, almost odorless substance. Its empirical formula is $C_{46}H_{77}NO_{19}$. Ultraviolet absorption spectra indicate a conjugated tetraene structure. This structure is new among antibiotics, although several other new antifungal agents derived from streptomyces give similar absorption characteristics. The molecule has weakly basic and acidic properties and forms unstable salts. It is administered on the basis of units. The U.S.P. requires not less than 2000 units per mg.

Nystatin is inactive against bacteria; it is most effective against the active growing stages of the yeast-like fungi. It is not effective against actinomycetes. This antibiotic is poorly absorbed from the gastrointestinal tract, and after oral doses of 500,000 units 3 times a day it exerts its effect against yeasts present in the lumen of the intestine.

Nystatin exhibits a low degree of toxicity on oral administration. In man, very large doses produce nausea, vomiting and diarrhea. No serious toxic or allergic reactions have been reported up to this time.

**Therapeutic use.** This antibiotic is used to prevent or treat intestinal moniliasis. The gastrointestinal distress, diarrhea and pruritis, vulvovaginitis, and thrush encountered with therapy with the broad-spectrum antibiotics have been linked to the overgrowth of the intestinal monilia, *Candida albicans*, by numerous workers. These fungal superinfections can be controlled by the oral administration of tablets of 500,000 units of nystatin 2 to 3 times a day.

Other uses for this antibiotic are being explored. It may be available for the treatment of such troublesome clinical conditions as generalized systemic moniliasis, coccidioidomycosis, blastomycosis, and histoplasmosis. Unless it is possible to administer nystatin in such a way that contact is achieved between the antibiotic and the monilial pathogen, the drug is not likely to be effective. The systemically absorbed antifungal antibiotics are more promising in this respect.

## Griseofulvin (Fulvicin, Grifulvin, Grisactin).

This antibiotic was isolated in 1939 from *Penicillium griseofulvum*. It was discarded in early studies because it did not possess anti-bacterial activity. Its effectiveness against fungi in both

plants and animals led Gentles (1958) to explore its use in intractable ringworm infections in man. This antibiotic represents a significant advance in the treatment of superficial fungus infections.

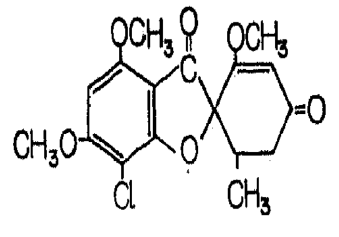
Griseofulvin is a colorless, slightly bitter, thermostable compound which chemically is 7-chloro-2′,4,6-trimethoxy-6′-methylspiro-[benzofuran-2(3H), 1′-[2]cyclohexene]-3,4′-dione.

Griseofulvin inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, nails, and skin, such as *T. rubrum*, *T. tonsurans*, *T. mentagrophytes*, *T. verrucosum*, *T. sulfureum*, *T. schoenleini*, *M. audouini*, *M. canis*, *M. gypseum*, and *E. floccusom*. Griseofulvin is not effective against bacteria, candidiasis (moniliasis), histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis (torulosis), malassezia furfur, or norcardiosis. Griseofulvin is indicated for the treatment of tinea capitis (ringworm of the scalp), tinea corporis (ringworm of the body), tinea pedis (athlete's foot), and tinea unguium (onychomycosis, ringworm of the nails).

**Toxicity and side effects.** In animals very large doses of griseofulvin administered orally do not produce fatalities. Chronic toxicity studies in several animal species have not demonstrated deleterious effects upon the important viscera unless massive doses are administered. Very large doses have produced unusual but reversible changes in the germinal epithelium in male rats when the antibiotic was injected parenterally. Interference with spermatogenesis persisted for as long as 10 days after the drug was administered. However, no changes were found in the testes or ovaries of animals receiving the drug orally for over a year in amounts greater than clinical doses.

Studies to determine the influence of griseofulvin on spermatogenesis in man have not indicated a decrease in sperm count, and testicular biopsies after 79 days of treatment with daily oral 2-gm. doses showed no abnormalities.

The most commonly reported side effects after oral doses of griseofulvin have been occasional instances of heartburn, nausea, epigastric discomfort, and diarrhea. A few patients have developed urticaria. Although griseofulvin is derived from a *Penicillium* mold, it does not appear to elicit sensitivity reactions in those patients known to be sensitive to penicillin. However, the possibility of cross-sensitivity reactions exists.



Griseofulvin

Hematologic findings of leukopenia and a depression of granulocytes following the administration of griseofulvin indicate that periodic blood cell counts are advisable. These blood changes, although relatively rare, should serve as a warning of potential drug toxic reactions. To date, the hematologic findings have returned to normal during continued drug administration or shortly after cessation of drug therapy. If granulocytopenia occurs, the drug should be discontinued.

Reports have been made of central nervous system effects which involve a confusion, exhilaration, and insomnia with an impaired motor performance. There appears to be an intolerance to alcohol while patients are under griseofulvin therapy. Occasional urticarial eruptions have been reported, and a more serious serum sickness-like reaction with fever, joint pain, lymphadenopathy, and joint swelling has also been observed. Because definitive knowledge of its effect on the fetus is lacking, administration of griseofulvin to pregnant women is not recommended.

**Clinical use.** When the antibiotic is administered orally in 0.5-gm. daily doses, it is absorbed from the gastrointestinal tract and deposited in newly growing cells of the skin, hair, and nails. The concentration is fungistatic, and fungi do not invade the new-formed cells. As new skin, hair, and nails are formed, they replace the fungi-infected keratin cells, which are shed.

Griseofulvin is administered orally 0.5 gm. daily in 2 or 4 divided doses. In severe, refractory *T. rubrum* infections, 0.75 to 1 gm. daily may be required initially and reduced to 0.5 gm. or less daily after the initial desirable subcutaneous effects have been obtained. The oral dosage for children is 10 mg./kg., which may be administered as a single dose or in divided doses. These doses are based upon the microcrystalline powder which provides higher plasma concentrations than other dosage forms (see page 122).

Dosage is continued for at least 2 weeks after the patient ceases to show clinical signs of the presence of fungi in the skin, hair, or nails or until repeated cultures prove negative.

Duration of treatment is important because the drug has an unusual mode of action. The length of therapy varies with the severity and site of the infection; in tinea pedis and capitis, 4 to 8 weeks may be adequate; in onychomycosis, 4 to 6 months may be required.

*Grisactin* is a minute crystalline form of griseofulvin that provides a more effective surface area for absorption. Blood serum concentrations produced by a 0.5-gm. dose are equivalent to the concentration obtained by 1 gm. of the dosage form of the original preparation.

It is generally conceded that the discovery of this very effective oral antifungal drug constitutes a major therapeutic achievement. It appears to be essentially nontoxic, easy to administer, and dramatically effective in infections that traditionally have been difficult, if not impossible, to cure. The use of griseofulvin in the treatment of fungus infections is discussed on page 217.

### Amphotericin B, U.S.P. (Fungizone).

Amphotericin B is a conjugated heptaene antifungal antibiotic produced by strains of *Streptomyces nodosus*. The antibiotic is a yellowish powder relatively insoluble in water. Solubilized preparations in the form of colloidal dispersions with sodium desoxycholate are suitable for intravenous injection. The outstanding characteristic of amphotericin B is its usefulness in systemic fungus diseases. It has a wide spectrum of fungistatic action against yeast-like fungi: *Coccidioides immitis*, *Histoplasma capsulatum*, *Candida albicans*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Blastomyces brasiliensis*, and *Sporotrichum schencki*. This antibiotic is not active against bacteria, protozoa, or viruses. Gale (1960) has shown that amphotericin B interferes with a critical metabolic pathway (glycolysis) in intact yeast cells but not in mammalian erythrocytes. This action may be related to the therapeutic effects of the drug.

Amphotericin B is poorly absorbed from the gut. It is injected intravenously, and demonstrable blood levels persist for 18 to 24 hours after a single injection. The drug is very slowly excreted from the body by the kidneys. The spinal fluid level is $\frac{1}{30}$ to $\frac{1}{50}$ that of the blood serum level.

**Therapeutic use.** In view of the potential toxicity of this antibiotic, it should be given only to hospitalized patients in whom a diagnosis has been confirmed by a positive culture of a susceptible mycotic infection.

The mycotic infections in which amphotericin B is effective have resisted chemotherapy for many years. While the clinical experiences up to the present time have been limited, the results have been very encouraging. In many cases arrest of the disease or apparent cure of serious systemic infections have been reported. In coccidioidomycosis, histoplasmosis, North American blastomycosis, systemic moniliasis, and mengineal cryptococcosis (torulosis), amphotericin B has been found effective in some cases but not all. The antibiotic has only limited value in South American blastomycosis. It is the drug of choice in infections caused by *Histoplasma capsulatum*, *Cryptococcus neoformans*, the coccidioides, and some forms of blastomyces. Hydroxystilbamidine may be a superior chemotherapeutic agent in treating some infections caused by strains of blastomyces (page 168). Potentially dangerous side effects that are associated with the required therapeutic doses necessitate close medical supervision of the patient.

Amphotericin B is slowly injected intravenously in the form of a dilute infusion of the drug in 5 per cent dextrose solution. The dry, sterile, lyophilized powder is dissolved in the dextrose solution to give a concentration of 0.1 mg. per ml. Saline solution causes the antibiotic to precipitate from solution and should not be used. The usual adult dose is 50 mg. daily. The initial dose is administered as 0.25 mg./kg. and adjusted to the tolerance of the patient. A course of treatment usually is from 20 to 60 days but may be longer if necessary. The solution of the drug causes pain at the injection site because the drug is irritating to the venous endothelium. Therefore, the injection site must be changed frequently.

The renal toxicity of amphotericin B is its most serious disadvantage. The blood urea nitrogen must be followed during therapy. The chief toxic effects which are encountered are fever, nausea, emesis, anorexia, and azotemia, with the appearance of cellular and granular casts in the urine as well as hematuria and proteinuria. Kidney function tests should be made at intervals during prolonged therapy. Kidney function impairment had returned to normal in most patients when the drug was discontinued.

### New Classes of Chemotherapeutic Agents

In an effort to broaden the scope of anti-bacterial attack against infecting microorganisms, many classes of synthetic organic compounds have been examined. A fundamentally different chemical was discovered by Lesher and associates (1962) with the synthesis of a series of naphthyridine derivatives. These compounds are not related chemically to the sulfonamides or to any of the known antibiotics.

### Nalidixic acid (NegGram).

Nalidixic acid is a naphthyridine derivative unrelated chemically to other types of chemotherapeutic agents. It is used in the systemic treatment of infections caused by gram-negative bacteria. Nalidixic acid is a pale yellow, crystalline substance, only slightly soluble in water but readily soluble in dilute alkali. It is 1-ethyl-7-methyl-1,8-naphthyridin-4-one-3-carboxylic acid.

Nalidixic acid is indicated in the treatment of gram-negative infections, especially in the genitourinary tract, caused by *Proteus*, *Escherichia coli*, *Aerobacter*, *Klebsiella*, and certain strains of *Pseudomonas*. The drug has been used successfully in treating infections caused by organisms that have become resistant to other anti-bacterial drugs. Most gram-positive bacteria are usually not sensitive *in vitro* to nalidixic acid, but some favorable clinical results have been reported. Disc sensitivity tests are recommended as a guide to bacterial sensitivity.

Nalidixic acid is rapidly absorbed from the gastrointestinal tract and subsequently excreted in the urine as the unchanged drug, a closely related compound, and conjugated derivatives. About 80 per cent of the ingested dose is recovered in the urine, and most of the excretion takes place within the first 8 hours. Repeated oral doses of 500 mg. 4 times daily for 5 consecutive days have been reported to produce a sustained, biologically active concentration of the drug in the urine. Biologically active levels of the drug were present in 8 subjects 1 hour after single oral doses of 1 to 4 gm.; anti-bacterial activity of the serum had largely disappeared after 6 hours.

Nalidixic acid appears to be well tolerated in various species of animals and man. Dogs are particularly sensitive, and high doses may produce convulsions in these animals. Clinical experience to date has demonstrated that the drug is not toxic to patients with impaired renal function. Blood urea nitrogen values of patients taking the drug have not been significantly altered. The side effects experienced by patients under medication with nalidixic acid are nausea, vomiting and other gastrointestinal disturbances, sleepiness, drowsiness, weakness, headache, and nonspecific pain.

Nalidixic acid may produce itching, pruritus, rash, and urticaria. Eosinophilia and a rise in the serum glutamic oxalic transaminase have been noted in a few patients. These changes disappeared when the drug was discontinued. Marked overdosage of the drug associated with predisposing factors have led to neurologic side effects. In these few cases the symptoms of central nervous system stimulation may not have been caused by the drug. Crystalluria or fungus overgrowth have not been observed in patients taking nalidixic acid.

Nalidixic acid has been used most extensively in treating genitourinary infections. It is most desirable to identify the sensitivity of the infecting organisms, and there has been a good correlation between the *in vitro* sensitivity and the subsequent clinical response. The drug may be administered concurrently with other anti-bacterial agents effective against gram-positive organisms. The availability of this new drug permits the physician to treat these difficult infections of the genitourinary tract more effectively. The anti-bacterial spectrum, the low toxicity, and the freedom from bacterial cross-resistance are significant advantages associated with the use of nalidixic acid.

The adult dose is 2 to 4 gm. daily administered as 500 mg. capsules in divided doses, depending on the severity of the infection. A daily dose of 4 gm. is recommended at the beginning of treatment to minimize the development of bacterial resistance. This dosage is continued for 2 weeks, and subsequent doses are 2 gm. daily.

### A Summary of Modern Anti-bacterial Chemotherapy

The current trends in therapy of the infectious diseases are recapitulated in this section. An attempt has been made to present the problems confronting the physician in the selection of the most satisfactory chemotherapeutic agent. Details of antibiotic therapy of specific diseases are considered in this and other chapters. The summary set forth here deals with the broader problems of chemoprophylaxis, hypersensitivity, anti-bacterial resistance, synergistic combinations, and the interpretation of sensitivity tests.

Table 10-2 indicates in a general way the choice of the major antibiotics or sulfonamides in a particular infection. There is disagreement as to whether or not a physician should prescribe these drugs without laboratory identification of the causative organism and its sensitivity. The therapeutic dilemma has 2 facets:

1. To achieve maximal benefit, treatment must begin early in the course of the infection.
2. Awaiting laboratory findings means the loss of valuable time.

As a partial solution to this dilemma, Dowling (1955) divided microorganisms into 3 groups with respect to their relation to infection, character of response to treatment, and frequency of appearance of antibiotic-resistant strains.

*Group 1* includes pneumococcus, meningococcus, β-hemolytic streptococcus, gonococcus, *Shigella*, and *Hemophilus influenzae*. This group usually responded promptly to adequate antibiotic therapy; resistant forms had not been found in patients at that time.

*Group 2* includes α- and γ-streptococci, coliforms, *Proteus*, Pseudomonas, *Micrococcus* (*Staphylococcus*), and *M. tuberculosis*. Infections by organisms of this group respond slowly to antibiotic therapy. Patients may improve and yet retain the organisms and the infection for years. Resistant forms have been encountered in patients.

*Group 3* includes *Brucella*, *Salmonella typhi*, and the rickettsiae. These infections respond quite promptly to antibiotic therapy, but they do have a tendency to recur; resistant forms do not develop, and the organism cultured during the recurrence is still sensitive to the original drug.

According to this approach, the problem of antibiotic resistance centers on the organisms of Group 2, chiefly the staphylococci, tubercle bacilli, and the gram-negative bacilli. Evidence is now available that strongly suggests that over the past decade strains of *N. gonorrheae* have evolved that are much less sensitive to penicillin (Simpson and Brown, 1962).

Essentially, this grouping of microorganisms holds today. The recently introduced antibiotics may be more effective against resistant strains of staphylococci, or the colistins may replace polymyxin B in pseudomonal infections, but the major groups of infections are still susceptible to the standard antibiotics.

Most physicians make a tentative diagnosis, take specimens for culture before therapy is started, and, pending a laboratory report, administer the drug most likely to benefit the patient if the tentative diagnosis is correct. *Whatever drug is selected must be administered in full therapeutic doses.* If the laboratory findings indicate an erroneous diagnosis, the medication can be changed. The patient will be no worse off than if no drug had been administered until the laboratory results were known. This approach would seem to be a reasonable compromise. Unfortunately, the reliability of laboratory sensitivity tests is not entirely trustworthy. In addition, Dowling (1957) contends that many patients have been treated with antibiotics who did not need these drugs, or were treated before a bacteriologic diagnosis was made. Such a procedure, he argues, delays proper diagnosis and makes it more difficult. "If antibiotic therapy must be resorted to, an accurate clinical diagnosis is imperative in cases in which laboratory data are not available."

An excellent critique of the laboratory control of antibiotic therapy has been written by Gould (1960). The bacteriologic problems are beyond the scope of this text, but the fact must be stressed that there is a paucity of correlating data between laboratory sensitivity tests, dosage schedules, and drug selection. Laboratory tests of the minimal concentrations of antibiotics required to inhibit growth of the infecting microorgansim are seldom helpful in determining the dosage of the drug. In some cases, clinical success may follow a laboratory report that the organism is resistant, although this is rare. With the current trend toward the employment of combinations of antibiotics, sensitivity tests may be seriously misleading. Authorities recommend that *in vitro* tests be done with antibiotics in any serious infection that has not responded promptly to therapy. If these tests indicate that a combination of two antibiotics produces complete killing of the microorganism, those drugs may be used. However, some combinations must be avoided, such as penicillin and chlortetracycline. These two antibiotics are antagonistic under certain conditions. There are very few clearly substantiated indications for antibiotic combinations, despite their wide use. *In vitro* and *in vivo* effects may be significantly different.

In certain disease states two antibiotics have been demonstrated to be superior to one administered alone. In enterococcic endocarditis, a combination of penicillin and streptomycin is generally accepted as most suitable. In brucellosis, combinations of streptomycin and one of the tetracyclines or chloramphenicol are used. In staphylococcic endocarditis, penicillin may be combined effectively with streptomycin or oxytetracycline. Other combinations of antibiotics have been reported as beneficial in certain instances, but these represent only a few highly selected conditions.

In laboratory tests the effect of one antibiotic *in vitro* can be inhibited to varying degrees by other antibiotics. The possibility of this occurring *in vivo* in patients cannot be overlooked. The problem is not one of treating bacteria but patients infected with the organism. This will require all the skill in the use of the chemotherapeutic agents that the physician can command.

There are very few controlled clinical trials with the various antibiotics and sulfonamides. As pointed out by Hewitt (1963), these tests are extremely arduous, and in clinical comparisons of similarly effective drugs, the therapeutic results may be indistinguishable. Such factors as toxicity, *in vitro* activity, ease of administration, or absorption may determine the choice of the drug. There is need for more accurately controlled clinical studies with the antibiotic agents.

For many infections the sulfonamides are superior to the antibiotics. For example, the merits of sulfadiazine in the treatment of meningitis have been stressed. The recently introduced, less toxic sulfonamides produce less drastic changes in the normal bacterial flora of the body than do the antibiotics. Although the problem of resistant strains will remain whether sulfonamides or antibiotics are used, the recent concern with emergent antibiotic-resistant forms of bacteria suggests that more consideration might be given to sulfonamide therapy.

There remains the final consideration of the use of these drugs in chemoprophylaxis. The role of penicillin in gonorrhea prophylaxis is well established. Sulfadiazine is superior in the prevention of *Shigella* dysentery. Chemoprophylaxis with these drugs in patients with rheumatic heart disease is an accepted fact. However, the warning against the tendency to employ these drugs without due regard to their attendant dangers must be made.

There is general agreement that antibiotics or sulfonamides are contraindicated in the prevention of secondary bacterial complications of diseases in which they are known to have no primary therapeutic effect, *e.g.*, the common cold, measles, influenza, chicken pox, and some other viral infections. The antibiotics are sometimes routinely used in chemoprophylaxis of many noninfectious disorders such as cerebrovascular accidents, comatose states, and burns. The evidence of the beneficial effects of such technics is lacking, and indeed the procedure may be harmful.

The problems of hypersensitivity and anaphylactic deaths from penicillin, the auditory deficits and vestibular complications of streptomycin and related antibiotics, the hazards of moniliasis, and the development of fatal staphylococcic enteritis indicate that the ideal therapeutic goals have not been reached. The physician must weigh these dangers when considering the drug to be prescribed. It appears that in spite of their extraordinary effectiveness, modern chemotherapeutic drugs require great skill and medical judgment in their clinical use.

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# 11

# *The Chemotherapy of Tuberculosis*

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Interest in the possibility of suppressing the growth of the tubercle bacillus and arresting the disease of tuberculosis dates from the discovery of this bacillus by Robert Koch in 1882. Koch described a peculiar small organism obtained from tubercles that was very difficult to detect; it offered unusual resistance to staining by ordinary aniline dyes and multiplied so slowly that often weeks elapsed before its growth became evident on culture media. This bacillus would cause tubercles to form in animal tissues; from these tubercles the organism could be recovered. Thus the way was opened for an attack upon the causative agent of tuberculosis, but the agents with which to fight this disease have been difficult to find. Waksman (1947) reviewed the microbiologic studies that have been made through the years leading to the discovery of streptomycin. The *fungi, bacteria,* and the *actinomycetes* all produce antibiotics active against *Mycobacterium tuberculosis.* A number of these antibiotics have been isolated and identified bacteriologically. None was sufficiently nontoxic, however, to warrant its use as a therapeutic agent until streptomycin was isolated. Feldman and Hinshaw (1944) first demonstrated the effectiveness of streptomycin in experimental tuberculosis. They were also the first to establish by clinical investigations the chemotherapeutic potentialities of this drug. These discoveries marked an important milestone in the struggle to achieve mastery of the disease tuberculosis.

Shortly after the discovery of streptomycin, Dr. Hinshaw commented upon the role of streptomycin therapy in tuberculosis as follows:

> "I believe we can successfully defend the statement that tuberculosis is, even in this enlightened age, the most important *infectious* disease of mankind. In Europe and in the Orient, tuberculosis is many times more frequent than in the United States, and the situation is steadily getting worse. But even in the United States during the recent

war approximately the same number of our citizens died of tuberculosis as were killed in battle.

"We are all told that the greatest of diseases are the degenerative diseases of middle and later life. We know that cancer and heart disease kill the most people. But these are diseases of older people while tuberculosis is a disease which is most destructive during the early years of adult life. Mary Dempsey has recently published some interesting figures. She points out that the average white woman may expect to live for 69 years. If she dies at the age of 24 from tuberculosis, instead of dying at 69, she has lost 45 potential years of life. On the other hand, if she should die at the age of 62 from cancer, she has lost but 7 potential years of life instead of 45. Dr. Dempsey states that in the aggregate, approximately 1.3 million potential years are lost by those who die of cancer. Those who die of tuberculosis also have lost approximately 1.2 million years of potential life. Even though the tuberculosis death rate has been so reduced in the United States of America that it is but one-third that of the cancer death rate, yet the potential years of life lost by these two diseases is very similar.

"Just what can we expect streptomycin to do in the fight against tuberculosis? This is the first drug to be made available which has real usefulness in the most important infectious disease affecting the human race. But there are many kinds of tuberculosis; many different diseases produced by tubercle bacilli and each offers special problems. Tuberculosis not only produces consumption of the lungs, it produces hunchbacks and is a frequent cause of other crippling deformities of the bones and joints of children and in adults, tuberculosis may destroy the kidneys or affect the intestines or cause peritonitis. There are forms of tuberculosis which were formerly regarded as 100% fatal prior to streptomycin, especially miliary tuberculosis which is spread throughout the entire body by way of the bloodstream and tuberculosis which affects the brain and spinal cord, the so-called tuberculous meningitis.

"Until the advent of streptomycin thousands of people died each year from miliary tuberculosis and tuberculous meningitis. Most of these are infants and young children. To make a diagnosis of miliary tuberculosis or tuberculous meningitis has always meant that early death was virtually certain. Already several hundred such patients have been treated with streptomycin and scores of these are well and perfectly normal. Many have died despite streptomycin treatment. Some of these were treated too late, some have died despite every effort. Some have improved for several months and later have succumbed to this most dreaded of diseases. But some have now remained well for two years and may be regarded as cured. Streptomycin is the only effective remedy in miliary tuberculosis and in tuberculous meningitis, and while it has not cured all, it is a very great remedy offering the first real hope in the treatment of a disease which was formerly almost universally fatal."

### Tuberculosis Therapy in the United States

A review of the status of tuberculosis therapy in 1964 indicates that there have been significant changes since Doctor Hinshaw's summary was presented 20 years earlier. There are now three important forms of therapy—streptomycin, isoniazid, and *para*-aminosalicylic acid. Current problems of treatment center around the most effective dosage schedules for these drugs. Since the introduction of chemotherapy there has been a 75 per cent reduction in deaths from tuberculosis in the United States. The average duration of hospitalization has been reduced from 2 years to about 6 months. The number of beds required for tuberculosis patients has been drastically reduced, with a resulting economic gain. Unfortunately, while the mortality rate of tuberculosis has declined rapidly, the number of new cases reported each year has not decreased at the same rate. In the United States tuberculosis continues to be a major public health problem, with more than 10,000 deaths annually and over 50,000 new cases each year (Perkins, 1963). Approximately 2 million persons in the United States in 1956 were ill or had been ill with tuberculosis. This is approximately the same number as was found in 1952. Approximately 2 million individuals were living in the United States in 1963 who had or had recovered from active disease, and over 30 million are estimated to be currently infected with living virulent tubercle bacilli (Perkins, 1963).

The conclusion must be reached that empty beds in the tuberculosis sanitarium do not mean that the disease is no longer important in this country. A certain degree of apathy toward a disease seems to be engendered by the discovery of spectacular chemotherapeutic agents. This has been true in the discovery of very effective antituberculosis drugs. A similar medical and lay public indifference developed with the discovery of the curative merits of penicillin in venereal disease. We have the means at hand for eradicating tuberculosis in the United States by the proper large-scale use of chemotherapeutic agents. This involves all aspects of detection and treatment of the disease. Whether we shall be wise enough to use this hard-won knowledge to its best advantage remains to be determined.

### Problems of World-Wide Tuberculosis Therapy

The tuberculosis death rate has been cut in half or has fallen even more sharply in many countries since 1952, according to a report from the World Health Organization. This development is believed to reflect the use of drugs in therapy and intensive tuberculosis detection. However, there is a time limit that is imposed by the acquisition of resistant forms of *Mycobacterium tuberculosis* resulting from the continued use of these drugs. It is unfortunate that streptomycin, *para*-aminosalicylic acid, and isoniazid have been used improperly, and drug-resistant organisms are now frequently encountered. It is possible to avoid the emergence of drug resistance in patients' bacilli by adequate therapy. Therefore, theoretically, it should be possible to use the present drugs indefinitely without encountering resistant strains. As will be shown, this matter constitutes the major issue in the present-day use of chemotherapeutic agents in tuberculosis. The continuing successful search for new drugs holds promise for the eventual control of the emerging resistant forms of *M. tuberculosis.*

## Experimental studies in tuberculosis chemotherapy.

In the years following the discovery of the sulfonamide drugs, research in the field of tuberculosis chemotherapy was very fruitful. The demonstration that sulfanilamide had an inhibitory action on experimental tuberculosis marked the beginning of this period. The succeeding years have seen the development of the *sulfones*, *streptomycin*, *para-aminosalicylic acid*, the *thiosemicarbazones*, *isoniazid*, and the recently introduced *tuberculostatic antibiotics*. A brief account of these experimental investigations is given in the sections dealing with the individual drugs. The development of improved experimental evaluation technics during this period has likewise contributed greatly to the chemotherapy studies (Grunberg and Prince, 1963). The experimentally infected mouse is now used as a quick and reliable test subject for primary screening of antitubercular agents. Isoniazid was first discovered using mice infected with a standardized culture of *M. tuberculosis* H37Rv. Antituberculosis drugs are also evaluated experimentally *in vivo* in guinea pigs and monkeys infected with tuberculosis. The experimental aspects of drug screening and chemotherapy have been reviewed by Robson and Sullivan (1963).

Unlike most other microorganisms, the tubercle bacilli are not readily wetted by water. The cell surface repels water. Consequently, in a culture medium using a water solution, populations of tubercle bacilli tend to grow in clumps or thick pellicles consisting of large numbers of organisms firmly adhering to one another. This peculiar mode of growth makes it difficult to prepare uniform bacterial suspensions for *in vitro* and *in vivo* anti-bacterial studies. It has been discovered that certain wetting agents, especially Tween 80 and Triton A-20, when added to the culture medium are capable of rendering the surface of the cells wettable by water. When transferred again to a solid or liquid medium without a surface-active agent, the organisms follow the characteristic pattern of growth. Under these conditions the characteristic *colonial morphology* of the *serpentine pattern of growth* remains unchanged, and the organisms do not lose their virulence. Some surface-active agents will impede the growth of tubercle bacilli. Long (1958) has suggested that there is reason to believe that new principles of therapeutic action will come to light as this field is explored.

The biochemical and biologic properties of *Mycobacterium tuberculosis* have been studied in great detail, utilizing the improved technics of electron microscopy (Willett, 1963). The finer details of the cell wall and the nature of the cytoplasm is under investigation. In addition to the basic cellular components such as fat, sugar, and proteins, complex macromolecules of lipoproteins and lipopolysaccharides are known. The specific concentration of these latter molecules in the cell and cell membrane and their physiologic functions are under study. Methods are available to isolate the cell wall for chemical analysis and morphologic identification. Findings from these studies will provide much valuable information that will be useful in understanding the mode of action of the antituberculosis agents.

Improved laboratory methods for the isolation of tubercle bacilli and identification of the antimicrobial agents most likely to provide a favorable clinical response have been devised by Morse, Weiser, and Kuhn (1960). These tests aid in identifying mycobacteria as such and in distinguishing tubercle bacilli from other pathogenic and nonpathogenic mycobacteria. The methods permit the isolation of *M. tuberculosis* in 21 to 28 days. Because definitive proof of tuberculosis in a patient is provided only by isolating the tubercle bacilli, it is desirable to make this analysis as rapidly as possible. In addition, improved methods of isolation of a culture of microorganisms peculiar to a patient make possible the determination of the best drug or drugs for therapy.

### STREPTOMYCIN

Descriptions of the administration of streptomycin and dihydrostreptomycin are given in the chapter on antibiotics. The use of these drugs in tuberculosis is quite similar; therefore they will be considered together in this section. Dihydrostreptomycin is used only rarely for tuberculosis therapy. It is employed in the few patients who cannot tolerate streptomycin.

The value of a drug in the treatment of tuberculosis is difficult to determine. Collaborative studies with antituberculosis drugs have been made on large groups of patients with all types of tuberculosis. The staffs of United States Army, Navy, and Veterans Administration hospitals have cooperated with other groups, under the leadership of the American Trudeau Society and the American College of Chest Physicians. The aim of these studies has been to determine the most satisfactory dose regimen of new drugs.

In general, the findings have indicated that streptomycin, in properly selected cases, can be expected to alleviate the symptoms of some of the most serious and distressing forms of the disease. The emergence of streptomycin-resistant strains of tubercle bacilli constitutes one of the most important limiting factors. The toxicity of streptomycin is an additional disadvantage. The inability of the antibiotic to have a favorable influence upon lesions with a large necrotic component is another disadvantage of streptomycin therapy.

#### Dose.

Clinical experience with streptomycin therapy has indicated that the best regimen for most patients is 1 gm. of streptomycin intramuscularly 2 or 3 times a week with 12 gm. of *p*-aminosalicylic acid or 150 to 300 mg. of isoniazid orally each day. Therapy must be integrated with the patient's resistance, the use of surgical measures, and the development of resistant forms of the organism. The dose of dihydrostreptomycin is the same as for streptomycin. Dihydrostreptomycin is preferred by some physicians for short-term therapy of 3 months or less.

Suggested dosage schedules for tuberculosis patients whose organisms are sensitive to streptomycin, *p*-aminosalicylic acid, and isoniazid are given on page 138.

In individuals exhibiting sensitivity to streptomycin, dihydrostreptomycin may be used without reaction. Bacterial resistance will not be prevented by this, as bacilli resistant to streptomycin are also resistant to dihydrostreptomycin.

Dosage must be adapted to specific individual problems, but most workers agree that therapy should continue for at least 12 months or longer for all patients and 18 to 24 months for those with more serious disease. Streptomycin and dihydrostreptomycin are most effective when combined with oral *p*-aminosalicylic acid or isoniazid administration.

*Mycobacterium tuberculosis* develops resistance to streptomycin and the other antituberculosis drugs with dismaying facility. By genetic mutations resistant forms evolve that do not again become sensitive to the drug. As treatment is prolonged, more and more patients yield resistant organisms. Under ordinary conditions of therapy with streptomycin alone in 1-gm. doses daily, over 75 per cent of patients will develop resistant organisms within 4 months. The significant role that other drugs play in tuberculosis therapy is the prevention of the emergence of resistant bacilli.

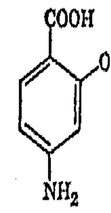
### *PARA*-AMINOSALICYLIC ACID

Bernheim (1941) observed that salicylic and benzoic acids increase the oxygen consumption and carbon dioxide production of the tubercle bacillus. He concluded that these acids are oxidized as metabolites by this organism and that compounds of a similar structure might also be metabolized.

Lehmann (1946), in Sweden, investigated a large number of derivatives of benzoic and salicylic acids in a search for a compound possessing bacteriostatic properties against *M. tuberculosis*. He found 4-aminosalicylic acid or *p*-aminosalicylic acid (PAS) most active. Bernheim found that PAS stimulated the metabolism of virulent bovine strains of tubercle bacilli. This was confirmed for pathogenic human-type organisms by Lehmann, who also discovered that nonpathogenic strains did not show an increased oxygen consumption. Lehmann made the significant observation that the ability of benzoic and salicylic acids to stimulate oxygen consumption was accompanied by an inhibition of growth and multiplication of the bacilli. The actual testing of the derivatives of these acids was made by noting the inhibitory effect of their presence on the growth of the tubercle bacilli *in vitro*.

After numerous unsuccessful attempts, Rosdahl, a Swedish chemist, was able to prepare a sufficient amount of PAS for Lehmann to conduct clinical trials with the compound. In 1944, PAS was first administered to man in the treatment of tuberculosis.

Lehmann found that the addition of a hydroxyl group or an amino group to benozic acid increased its growth-inhibiting effect, and that the position of these radicals was of great importance. Of the various hydroxy benzoic acids, *ortho* (salicylic acid) was most effective, while the *meta* showed less effect, and the *para* compound the least. On the other hand, of the amino derivatives of benzoic acid, the *o* and *m* compounds were less active than *p*-aminobenzoic acid. When the most favorable positions were combined in 1 molecule, 4-amino-2-hydroxybenzoic acid (*p*-aminosalicylic acid) was formed, and this compound was found to be far more effective in inhibiting the growth of tubercle bacilli than any other combination.



Aminosalicylic Acid, U.S.P. (PAS)

Because of the instability of PAS and the difficulty of obtaining a pure compound, discrepancies appear in the literature regarding its physical, chemical, pharmacologic, and therapeutic properties.

**Aminosalicylic Acid, U.S.P. (Pamisyl, Para-Pas, Parasal, Rezipas).** PAS is a white, crystalline powder. It is soluble in distilled water to the extent of 0.2 per cent. It is moderately soluble in alcohol or ether and readily soluble in NaOH solutions, forming the monosodium salt. PAS solutions in water exhibit a pH of 3.5. The taste of PAS is mildly sour. There may be a bitter after-taste. Certain preparations may be quite disagreeable or nauseating. To prevent oxidation, PAS should be stored in a cool, dry place protected from light. The drug is supplied in tablet dosage forms of 0.3, 0.5, and 1.0 gm.

**Sodium Aminosalicylate, U.S.P.,** is soluble in water to the extent of 1 gm. in 2 ml. The pH of the solution is between 6.5 and 8.5. Like PAS, solutions of the sodium salt should be used within 24 hours after preparation. *Under no circumstances use a solution if its color is darker than that of a freshly prepared solution.* Sodium Aminosalicylate Tablets, U.S.P., are available, which contain 0.5 gm. of the drug.

**Potassium Aminosalicylate (Paskalium, Paskate, Parasal Potassium)** is a very soluble salt of aminosalicylic acid. There is some evidence that the potassium salt may cause less gastric irritation than the other forms of PAS. It can be used in tuberculosis patients on a restricted sodium diet.

**Calcium Aminosalicylate (Pasara Calcium)** is a water-soluble salt of aminosalicylic acid. Its chief role is for administration to patients on a restricted sodium diet.

#### Tuberculostatic activity.

Virulent human strains of the tubercle bacilli are susceptible to PAS *in vitro*, and in addition, the oxygen consumption of these organisms is increased. *The inhibitory effect is bacteriostatic, not bactericidal, and the staining properties of the organism are not affected.* The concentration of PAS necessary to inhibit growth of the tubercle bacilli varies from 1 to 10 mcg./ml., depending upon the strain of organism and the conditions of the test (Bogen, 1950).

The inhibitory effect of PAS is not depressed by the presence of serum but it is markedly decreased by increasing the number of organisms in the inoculum. The inhibitory effect is increased by Tween 80. The tubercle bacilli will develop resistance to PAS, and clinical experiences with this drug indicate that it is most effective in combination with other drug therapy.

#### Absorption, distribution, and excretion.

Way *et al.* (1948) determined the metabolism of PAS in rats, dogs, and humans, and established that the drug is rapidly and totally absorbed and rapidly excreted when administered orally. Within 10 hours, 85 per cent of it can be recovered in the urine in the free form and as conjugated amines. In the rat the highest concentrations of the drug were found in the kidneys, lungs, and liver. In man, the drug is absorbed after an oral dose to give a peak plasma level within 1 hour. Within 7 hours, 85 per cent of the dose is accounted for in the urine. Man shows a high tendency to conjugate PAS; 60 per cent of the total dose was recovered from the urine as 1 or more amine conjugates by these workers. The chief biotransformation products are *p*-aminosalicyluric acid and *p*-acetylaminosalicylic acid. The following compounds were isolated from the urine: unchanged PAS (14 to 33 per cent); acetyl *p*-aminosalicylic acid (28 to 63 per cent); *p*-aminosalicyluric acid (0 to 26 per cent); 2 unknown free amines (2 to 10 per cent); and 1 unknown bound amine (3 to 10 per cent). Thus PAS is metabolized principally by acetylation, but glycine conjugation occurs. The acetylation of PAS may be significant when this drug is combined with isoniazid therapy. This factor is discussed in considering the excretion of isoniazid and combined drug therapy.

Chemical methods that can be used to determine blood or urine concentrations of PAS are available. Under usual conditions of therapy the amount of the drug in the blood is not determined. A very satisfactory method for determining PAS as well as isoniazid blood levels has been developed by Leifheit and Smith (1959). This method is simple and may be used as a guide in the chemotherapy of tuberculosis with these drugs.

### Toxicity.

According to the experiments of Bogen (1950), PAS is not acutely toxic to animals. Chronic toxicity experiments have shown that the drug can be taken by mouth in large doses by animals without ill effects.

In man, the side effects noted during PAS therapy are nausea, vomiting, and diarrhea. Sodium bicarbonate or aluminum hydroxide suspension has been found to reduce the gastric irritation. Allergic reactions have been reported. These are usually a mild generalized pruritis or dermatitis that responds to antihistaminic therapy.

Doses as low as 8 gm./day have been reported by some workers to produce toxic effects. Others have given 3 times this amount without ill effects. Lehmann suggested a dose of 10 to 15 gm./day, and most reports have indicated that this dosage is free from objectionable side effects.

A number of reports have been made of cases of myxedema, toxic hepatitis, and disturbances of carbohydrate metabolism occurring during treatment with PAS. In view of these findings, individuals exhibiting minor toxic symptoms during the course of treatment with PAS should be carefully watched.

### Therapeutic use.

Extensive clinical investigations have indicated that PAS is valuable for the treatment of tuberculosis. Most reports have commented upon the early symptomatic improvement following the use of this drug. These have been characterized by a tonic effect with an *improved general condition* and *increase in appetite, improved tissue turgor, less cough* and *a lesser amount of sputum, slowing of the pulse and respiration, an increase in vital capacity* and *increase in hemoglobin*. A fall in body temperature has been noted, especially in patients with a high fever. The temperature drop is not associated with a salicylate effect but is related to the infection.

PAS is not sufficiently superior to streptomycin to warrant substitution for the latter drug. However, PAS has been used in patients whose tubercle bacilli have become resistant to streptomycin. In these cases the drug is of value. It appears, therefore, that *PAS is a therapeutically useful drug in pulmonary tuberculosis, especially in patients from whom streptomycin is withheld for any reason.* The principal use of PAS is to supplement therapy with streptomycin and isoniazid. It serves to provide additional chemotherapeutic effects and helps prevent the development of resistant forms of the bacilli.

### Dose.

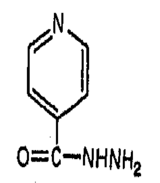
PAS is given orally, usually in a dose of 8 to 16 gm./day, along with streptomycin therapy. The total daily dose is administered with food and divided into 4 or 5 doses. It may be administered as a flavored effervescent drink along with sodium bicarbonate. The rapid urinary excretion necessitates frequent dosage. The drug should be administered orally every 3 or 4 hours in order to maintain a blood level high enough to provide clinically effective amounts. A maximum blood level of 10 mg./100 ml. is attained after a single oral dose of 4 gm.; doses of 2.5 gm. every 6 hours are sufficient to maintain this level.

## ISONIAZID

During the course of synthesis of the thiosemicarbazone of isonicotinaldehyde as an antituberculous compound, Fox (1951) used isonicotinic acid hydrazide as an intermediate. This chemical intermediate was subsequently found to exert a striking effect on experimental tuberculosis in mice. Grunberg and Schnitzer (1952), Bernstein *et al.* (1952), and others made a careful chemotherapeutic survey of compounds related to isonicotinic acid hydrazide and found 1-isonicotinyl-2-isopropyl hydrazine (iproniazid) to be the only one that was as effective as isonicotinic acid hydrazide itself. Subsequent clinical experiences with these drugs have indicated that isonicotinic acid hydrazide, *isoniazid,* is superior in human tuberculosis.

**Isoniazid, U.S.P. (Nydrazid, Rimifon, Tyvid, Amazide, Cotinazin, Dinacrin, Ditubin, Niconyl, Nicozide, Tisin)** is a colorless, crystalline solid, essentially tasteless and odorless. It is freely soluble in water and sparingly soluble in alcohol. The dry solid is stable. As a chemical entity it was reported in the German chemical literature of 1912 by Meyer and Mally. The drug is commonly referred to in the literature as INH.

According to Bernstein *et al.* (1952), isoniazid had the highest activity against tubercle bacilli *in vitro* of all drugs that had been tested by that date. The M.E.D. is 1/100 that of PAS in murine tuberculosis in mice. Its activity against other microorganisms is very low.



Isoniazid, U.S.P.

The first trials with isoniazid in human tuberculosis were carried out in 1951. The dramatic therapeutic effects of oral isoniazid medication were clearly evident.

### Absorption, distribution, and excretion.

In experimental animals, isoniazid is rapidly absorbed from the gastrointestinal tract. Peak levels in the plasma occur within 1 hour after an oral dose of 3 mg./kg. The major portion of the drug is excreted in the urine in 24 hours, and very little remains unabsorbed. Isoniazid is distributed relatively uniformly in blood plasma, spinal fluid, and into such tissues as brain, liver, lung, and spleen (Rubin and Burke, 1953).

Yard and McKennis (1962) showed that the metabolism of isoniazid in man is different from its metabolic fate and excretion in the dog. Isoniazid is converted by man to 1-acetyl-2-isonicotinylhydrazine, then to acetylhydrazine, and finally to 1,2-diacetylhydrazine. Apparently the dog is incapable of forming and excreting 1,2-diacetylhydrazine. The chief metabolic product in the monkey and man is 1-acetyl-2-isonicotinylhydrazine (Hughes, 1953).

Considerable confusion has developed in the literature dealing with the fate of isoniazid in man. Analytic methods have only recently been developed that allow the accurate determination of isoniazid and its acetyl derivatives. In addition, difficulty has been experienced in correlating chemical analytical values with biologically active isoniazid serum levels. To compound the confusion, the degree of acetylation of isoniazid varies markedly from patient to patient.

In 1955, Hughes *et al.* reported that human subjects exhibited strikingly different capacities for metabolizing isoniazid and that an inverse relation existed between the extent of metabolism and the concentration of the drug in the blood. Isoniazid is converted in human subjects into several derivatives: hydrazones, isonicotinic acid, and acetyl isoniazid. The pyruvic acid and keto-glutaric acid hydrazones of isoniazid have been identified in the urine; they have not been determined in the blood. The early chemical methods for isoniazid did not distinguish between isoniazid and the biologically inactive acetyl derivatives (Morse *et al.*, 1956). Therefore, the data reported in the literature using the spectroscopic absorption method of Kelly and Poet (1952) must be corrected for this fact, which explains why some workers have not found evidence for a relationship between the therapeutic response to the drug and the concentration in the serum of patients.

Peters (1960b) developed a highly specific fluorometric method for measuring isoniazid in serum. The method is as sensitive as the microbiologic technics and more accurate (Peters *et al.*, 1961). The availability of this method has helped to solve many of the perplexing problems of the chemotherapeutic use of isoniazid.

After isoniazid administration, the body fluids, *e.g.*, sputum, urine, cerebrospinal fluid, plasma, and pleural exudate, exhibit antituberculous activity. The drug does not accumulate in body tissues upon prolonged administration. It is rapidly and almost completely absorbed from the gastrointestinal tract of man. The maximal serum concentration occurs approximately 1 to 2 hours after oral administration, and the greater part of a single dose is excreted in 24 hours in the urine.

It is clear that individuals have different metabolic and excretion patterns for isoniazid. These facts have therapeutic significance (Harris, 1963; Price Evans *et al.*, 1960). It is recognized also that the serum levels of biologically active INH are relatively constant in the same individual when he is tested repeatedly over a period of time. It is possible to divide a population of patients into two major groups, "rapid inactivators" and "slow inactivators." In the former, the blood serum levels are 0.2 mcg./ml. or less; in the latter, the levels are 0.8 mcg./ml. or greater after doses of 3 to 5 mg./kg. orally. A small group of patients (approximately 7 per cent) are classed as "intermediate inactivators" and exhibit blood serum levels of approximately 0.4 mcg./ml.

Rapid inactivation is related to the formation and excretion of acetylisoniazid in the urine. The existence of a genetic basis for these two phenotypes has been proved. Rapid inactivation of INH is inherited as a Mendelian autosomal dominant trait. The gene incidence varies among individuals of different races. For example, almost all Eskimos and Japanese, both native and American born, are rapid inactivators (Harris, 1963). Only approximately one-half of American patients of Northern European ancestry are rapid inactivators of isoniazid.

When INH is used alone in tuberculosis chemotherapy, the rate of inactivation is a very important factor in determining the dose and the frequency of administration. As is pointed out in the discussion of combined drug therapy regimens, the simultaneous administration of PAS introduces still another factor that may modify the excretion pattern of INH.

Mandel *et al.* (1959) employed microbiologic assays for the antimicrobially active INH and streptomycin in serum to measure the relationship between drug blood levels and therapeutic responses. They concluded that the serum level can be used as a basis for estimating the concentration of INH delivered to the multiplying bacilli in the body cavities. The availability of the newer fluorometric analytical technics for INH should assist in the solution of this laboratory and clinical dilemma. Authorities differ regarding the most satisfactory anti-bacterial blood level of isoniazid and other drugs for tuberculosis patients. The newer analytical methods that have been described should help to resolve this problem. The quantitative chemical method of Leifheit and Smith (1959) that makes possible the determination of free isoniazid and total isoniazid, as well as the *p*-aminosalicylic acid level in blood serum, will assist in placing therapy with those drugs on a more satisfactory basis.

### Bacterial resistance.

Shortly after the first clinical trials with isoniazid, the experimental production of resistant tubercle bacilli *in vitro* was carried out by growing these organisms in a medium containing the drug. Resistant strains can be recovered from patients undergoing isoniazid therapy for tuberculosis. Unfortunately, the appearance of these resistant strains has occurred within a few weeks of therapy. Recognizing this threat to effective chemotherapy with isoniazid, various authorities have warned that this drug must be employed with caution. Like the other drugs employed in tuberculosis therapy, it must be used as an adjunct to other well-established measures. Isoniazid is bactericidal against multiplying tubercle bacilli; however, it must be considered as bacteriostatic against resting cells.

Isoniazid-resistant strains of tubercle bacilli may develop during therapy for cavitary pulmonary tuberculosis. These strains are of interest, for they have lost much of their virulence for laboratory animals. This loss of virulence apparently is related to the lack of production of catalase by these strains. This modification of the tubercle bacilli does not reduce their virulence for man, since patients harboring these strains may show a progression of their disease. There is a controversy over whether or not catalase enzyme deficiency is fundamentally concerned in virulence. It appears that isoniazid-resistant, catalase-negative tubercle bacilli are highly attenuated for man. In most instances where

spread of the disease has been attributed to these strains, careful quantitative bacillary laboratory studies have shown that mixed populations exist, *i.e.*, populations of isoniazid-susceptible, catalase-positive bacilli and isoniazid-resistant, catalase-negative mutants. The susceptible catalase-positive bacilli cause the progression of the disease in man.

### Toxicity.

Large doses of isoniazid administered to laboratory animals produce reversible symptoms of central nervous system stimulation and liver and kidney damage.

The administration of the usual therapeutic dose of 3 to 5 mg./kg./day in man has not often produced toxic reactions. Isolated instances of intractable asthma, persistent hypotension, and increased susceptibility to the effects of other drugs, *e.g.*, epinephrine and ephedrine, have been reported in patients receiving isoniazid therapy. However, the causal relationships have not been clearly established. Untoward effects have been reported consisting of *hyperreflexia*, *constipation*, *postural hypotension*, *dizziness*, *difficulty in starting micturation*, *eosinophilia* and the *appearance of casts*, *albumin*, and *reducing substances in the urine*.

In the presence of renal disease isoniazid should be administered with care, since the drug is excreted chiefly by the kidneys. In cases of renal tuberculosis, the blood level may be followed and will serve as a guide for adequate dosage.

Isoniazid is capable of precipitating convulsive seizures in patients with epilepsy. In these persons the anticonvulsant drug dosage must be increased during isoniazid therapy.

### Isoniazid and pyridoxine metabolism.

Biehl and Vilter (1954) observed that large doses (16 to 24 mg./kg./day) of isoniazid produced a high incidence of *peripheral neuritis*. Symptoms of *bilateral peripheral paresthesia*, *numbness*, *burning pain*, and *weakness* were reported by patients receiving these large doses for as long as 5 weeks. The symptoms disappeared promptly when the drug was withdrawn. The similarity of the neuritis to that produced by the vitamin $B_6$ antagonist desoxypyridoxine led them to investigate $B_6$ metabolism in tuberculosis patients on isoniazid therapy. They found a direct relationship between the dose of isoniazid and the vitamin $B_6$ excretion in the urine. The administration of 50 to 450 mg. of pyridoxine with 20 mg./kg. of isoniazid daily prevented the development of the neuritis. A similar observation was made by Oestreicher *et al.* (1954). These workers suggest that isoniazid neuritis is at least in part a manifestation of vitamin $B_6$ deficiency. The hypothesis is advanced that isoniazid depletes the tissues of $B_6$ by the formation and excretion of isonicotinyl hydrazone of pyridoxal. This phenomenon is of general interest because it illustrates an unusual hazard of drug therapy. Apparently the chemotherapeutic effect of isoniazid is unrelated to its vitamin-like association with nicotinamide (Fox, 1951).

### Dose.

The dosage range of isoniazid is from 3 to 5 mg./kg./day, given in 2 doses at 12-hour intervals. The drug is supplied in tablets of 100 mg. and the usual adult dose is 1½ to 3 tablets per day. The ease of administration, lack of serious drug toxicity, patient acceptance, and low cost are noteworthy advantages. When isoniazid is used alone, drug resistance is the serious problem. Therefore, the most satisfactory clinical experiences have been obtained by combined therapy with other drugs. The vitamin $B_6$ deficiency induced by isoniazid administration can be prevented by the administration of pyridoxine in doses of 50 to 100 mg. daily.

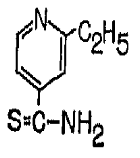
**Iproniazid (Marsilid).** The only derivative of isoniazid that has been found to possess significant activity and has been studied clinically is iproniazid (1-isonicotinyl-2-isopropylhydrazine). This congener is more toxic than isoniazid and produces psychotic reactions in doses of more than 8 mg./kg. daily. If iproniazid is used in tuberculosis therapy, the dose must be carefully regulated to avoid toxic symptoms. The early trials of iproniazid in mental illness are considered in Chapter 32.

## ETHIONAMIDE

**Ethionamide (Trecator)** is used in tuberculosis chemotherapy in patients who harbor tubercle bacilli resistant to isoniazid or in patients who cannot tolerate other antituberculosis drugs.

Ethionamide was synthesized in 1956 by Libermann *et al.* It is active *in vitro* and *in vivo* against *M. tuberculosis* resistant to isoniazid.

The substance is a yellow, crystalline, water-insoluble compound with a faint sulfite odor. It is 2-ethyl thioisonicotinamide.



Ethionamide

Ethionamide administered orally to mice has an $LD_{50}$ of 1000 mg./kg., as compared with an $LD_{50}$ of 200 mg./kg. for INH. *In vitro*, ethionamide is reported to be 2 times as active as streptomycin and 10 times less active than INH against test strains of *M. tuberculosis.* Tubercle bacilli can readily develop resistance to the drug *in vitro* and *in vivo* when it is used alone. In experimental animals ethionamide combined with streptomycin will produce a continuous decrease in the number of bacilli without evidence of emergence of resistant strains of microorganisms.

A number of clinical reports have appeared on the therapeutic effects of ethionamide. It is too early to determine the exact place of the drug in tuberculosis therapy, but it appears to be useful as a secondary drug in the treatment of the increasingly large number of patients who have developed organisms resistant to INH. Petty and Mitchell (1962) found ethionamide and pyrazinamide effective when combined with INH in some patients undergoing a retreatment regimen. In the U. S. Veterans Administration study (1961) a significant benefit was obtained by using ethionamide, 0.5 gm. orally once daily, in combination with either pyrazinamide, cycloserine, or kanamycin. Therapy was confined to patients who had all received prior chemotherapy and had proven cavitary disease as well as a positive sputum test resistant to INH and streptomycin. Most patients who are not converted to negative will produce organisms resistant *in vitro* to ethionamide within 4 to 6 months. Chaves *et al.* (1963) found that 20 per cent of a group of 54 chest clinic patients unresponsive to standard drug regimens achieved reversal of infectiousness within one year of treatment with a combination of ethionamide and cycloserine.

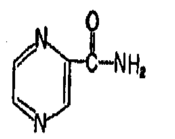
**Dose.**

Following a determination of the susceptibility of the patient's organisms to available drugs including ethionamide, the treatment may be initiated. In general, the highest tolerated dose has been used to avoid the risk of a rapidly developing resistance. In the adult, divided oral doses of 0.5 to 1.0 gm. daily have been used. Gastrointestinal disturbances usually limit the amount of the drug the patient can tolerate. Ethionamide therapy is not used alone.

Side effects most frequently encountered are gastrointestinal intolerance, comprising anorexia, a metallic taste in the mouth, nausea, vomiting, sialorrhea, upper abdominal discomfort, and diarrhea. Mental depression has been reported in some cases. Other effects produced are headache, acne and drug rash, jaundice, and peripheral neuritis. It should be pointed out that ethionamide is always used in conjunction with other drugs; therefore, it is impossible to determine the exact cause of untoward toxic effects. In addition, the drug has been used in patients who are in poor physical condition and suffering from a grave disease. If ethionamide is only effective in a small percentage of patients who cannot be treated satisfactorily by other drugs, the relatively mild side effects cannot be considered too high a price to pay for the benefits achieved in these patients.

### PYRAZINAMIDE

**Pyrazinamide (Aldinamide)** may be considered as a synthetic drug related to isoniazid. The compound is pyrazinoic acid amide.



Pyrazinamide

Pyrazinamide is a white, crystalline powder, stable at room temperature and readily soluble in water. Its antituberculosis potency in mice lies between that of PAS and of streptomycin. In combination with isoniazid, it is very effective in experimental tuberculosis in mice.

In clinical trials the immediate therapeutic effect is frequently very striking. However, the drug may cause hepatitis, especially when used daily in doses in excess of 35 mg./kg., and resistant organisms emerge rapidly. At the present time pyrazinamide is only used in seriously ill hospitalized patients with tuberculosis unresponsive to other chemotherapeutic agents. It appears that pyrazinamide is a drug of exceptional potency; yet its toxicity seriously limits its usefulness.

The oral adult dose of pyrazinamide is 35 mg./kg. in 3 or 4 divided doses daily.

### VIOMYCIN

A general description of this antibiotic is given in Chapter 10. Viomycin has been used in the chemotherapy of tuberculosis most successfully when prescribed in combination with streptomycin, dihydrostreptomycin, PAS, or isoniazid. While the antibiotic exhibits a marked ability to inhibit the growth of *M. tuberculosis*, the toxicity to the eighth nerve and renal toxicity limit the dose that may be used.

The recommended dose of viomycin sulfate is 2 gm. in terms of the base, administered intramuscularly every third day. The drug is provided as a sterile powder of viomycin sulfate in vials equivalent to 1 gm. of the base. The individual dose is divided into equal parts injected at 12-hour intervals. The solution for injection is prepared by dissolving the drug in 2 ml. of sterile distilled water. Solutions of viomycin may be stored at refrigerator temperature for a period of one week without significant loss of potency.

Combined therapy with viomycin and PAS or streptomycin is more satisfactory than medication with viomycin alone. Viomycin has been shown to be useful in streptomycin-resistant cases. The toxicity of viomycin markedly limits the effectiveness of this antibiotic in tuberculosis chemotherapy. The renal and auditory toxicity are discussed in the chapter on antibiotics.

### CYCLOSERINE

The properties of this antibiotic are described in Chapter 10. It is rapidly absorbed orally and produces high concentrations in the blood, urine, pleural fluids, and spinal fluid. Under laboratory conditions tubercle bacilli resistant to either streptomycin, PAS, or isoniazid are inhibited by cycloserine. This antibiotic should only be used for severe pulmonary tuberculosis in those patients who fail to respond to other tuberculostatic agents or who are infected with strains resistant to these drugs. Cycloserine is less effective than streptomycin or INH in producing desirable therapeutic benefits in patients.

Cycloserine is toxic in the usual therapeutic doses, and it is desirable to follow the blood levels in order to maintain an adequate tissue concentration and at the same time to prevent untoward effects. These include headache, lethargy, psychotic episodes, vertigo, and convulsions. Doses in excess of 1 gm./day may cause petit mal or grand mal seizures in some patients. These central nervous system effects may be controlled by the administration of sedatives, anticonvulsive agents, or pyridoxine. The undesirable side effects may appear after 1 to 2 weeks of therapy; they disappear when the drug is discontinued. Patients with a history of epilepsy or renal insufficiency are not good candidates for cycloserine therapy.

Cycloserine is administered orally in initial doses of 0.25 gm./day for the first 2 weeks. This dose is increased to 0.5 gm./day for 10 days and then to 0.75 gm./day if the side effects do not prohibit the increase. The maximum daily dose is 1 gm./day. The blood level should be maintained between 25 and 30 mcg./ml., if possible. The most satisfactory dosage schedules of cycloserine with INH, streptomycin, pyrazinamide, and viomycin have not been developed.

### KANAMYCIN

Kanamycin is effective in tuberculosis as a single drug and has been shown to be active against streptomycin-resistant strains of tubercle bacilli. Unfortunately, this antibiotic exhibits renal and eighth nerve toxicity. Clinical trials with kanamycin are now being made, and its place in the therapy of tuberculosis will become clear. The rapid appearance of strains of bacilli highly resistant to kanamycin makes it obvious that prolonged usage must be accompanied by the administration of other antituberculosis drugs. Dosage schedules are given in Chapter 10.

### THE SULFONES AND THIOSEMICARBAZONES

In a study of the sulfonamide drugs, Domagk *et al.* (1946) discovered that *sulfathiazole* and *sulfathiodiazole* exhibited a limited degree of activity against the tubercle bacillus. In 1943 the sulfones *Promin*, *Diasone*, and *Promizole* were shown to be effective in experimental tuberculosis. The interesting observation was made that these substances were effective in rat leprosy, and the drugs were employed in human leprosy in the United States.

In experimental tuberculosis, the activity was neither dependent upon sulfonamide or sulfone groups nor upon the thiazole or thiodiazole rings, but upon an open, chain-like arrangement of the nitrogen and sulfur atoms such as is present in the thiosemicarbazones.

After numerous trials, Promin, Diasone, and Promizole were found to be inferior to other chemotherapeutic agents in tuberculosis and are no longer used in this country.

Of the large number of thiosemicarbazones synthesized and investigated pharmacologically, one proved to be most effective. This was an acetylaminobenzaldehyde thiosemicarbazone called *Conteben* in Germany and *Tibione* and *Myvizone* in the United States.

### Antituberculous activity of amithiozone (Tibione).

Most of the experimental investigations leading to the development and clinical use of amithiozone were carried out in Germany. *In vitro* amithiozone inhibits the growth of the tubercle bacilli in concentrations as low as 1:200,000. The effect of amithiozone is much like that of PAS in experimental tuberculosis in guinea pigs.

In the clinical trials in Germany with *Conteben* on more than 10,000 patients with different types of tuberculosis, it was more successful in patients with lesions associated with a perifocal inflammatory process. The more recent the lesion and the better the blood supply, the more promising was the therapeutic response. *Miliary tuberculosis and tuberculous meningitis were not influenced by the drug.* Chronic pulmonary tuberculosis responded much less satisfactorily than the acute form.

In the United States, amithiozone has been studied by a number of investigators. The experiences indicated that this drug is definitely less effective than streptomycin. Its tuberculostatic effect appears to be similar to that of PAS, but it is more toxic.

## SUMMARY OF THE CHEMOTHERAPY OF TUBERCULOSIS

### Combined drug therapy.

Authorities differ regarding the most satisfactory combination of drugs for chemotherapy of tuberculosis. However, it is clearly established that the most desirable regimen involves the use of two or more drugs given concurrently for a long time. The demonstrated differences between the various regimens of combined therapy of streptomycin-PAS, streptomycin-INH, INH-PAS, and streptomycin-PAS-INH are not sufficient to indicate a superiority of any combination for all varieties of tuberculosis. Some clinicians avoid multiple drug administration for as long as possible in order that a reserve chemotherapeutic agent will be available to combat the resistant forms of the organism when they emerge. The combination of streptomycin-INH-PAS seems to be the specific therapy of choice in adults with tuberculous meningitis or miliary tuberculosis.

Crofton (1960) states that good chemotherapy for tuberculosis patients with strains of organisms sensitive to streptomycin, PAS, and INH requires the use of three drugs. In hospitalized patients under the age of 40 he employs 1-gm. doses of streptomycin daily, plus 5 gm. of PAS 3 times daily, plus 100 mg. of INH twice daily. In patients over the age of 40, the dose of streptomycin is reduced to 1 gm. 3 times weekly, plus the same daily dosage of the other two drugs. The object of this intensive therapy is to prevent the emergence of drug resistance. In his opinion, new drugs must be tried only on patients with resistant strains of tubercle bacilli that do not respond to streptomycin, PAS, or INH. Meticulous resistance tests should be carried out on a number of cultures from these patients. No potentially useful drug should be employed until it is certain that the organisms are susceptible to it. The new agent must be given in combination with other drugs that have the best chance of being effective in preventing the growth of resistant mutants.

The nature of the apparent potentiation of drug effectiveness in tuberculosis therapy achieved by drug combinations is unknown. Long (1958) has postulated that PAS reinforces the action of INH by preventing the body's inactivation of this potent drug. In fact, the greatest value of PAS lies in its ability to supplement the action of more potent agents. McDermott (1962) has reviewed other concepts of the mechanism of action of the enhancement of anti-bacterial effects by multiple drug use. He proposes that in two-drug therapy both drugs act upon the same organisms and not upon genetically resistant varieties of the microorganism.

There is evidence that the dose of isoniazid must be adjusted to the acetylation capacity of the individual patient. As has been stated, effective therapy is predicated on this fact. Since PAS is subject to acetylation, it has been demonstrated that the simultaneous administration of INH and PAS increase the serum INH level (Morse *et al.*, 1956; Mandel *et al.*, 1956). Peters (1960a) was unable to repeat these findings. It is not known at the present time whether this metabolic competition is of significance in the use of these two drugs simultaneously in tuberculosis therapy (Harris, 1963). Increasing the dose of INH does not bring about a striking improvement in the effectiveness of the drug. By contrast, combined INH and PAS therapy produces a marked benefit in the majority of patients.

There is a secondary place in tuberculosis therapy for the other antituberculosis drugs, but none has replaced streptomycin, INH, and PAS. A regimen of 300 mg. of INH plus 12 gm. of PAS daily appears to be the choice for the initial treatment of new cases of pulmonary tuberculosis. While streptomycin plus INH is more effective, its superiority is not so much greater as to outweigh the practical advantages of the oral dosage of INH plus PAS. As has been described, all three drugs may be used and the medication selected on an individual basis as therapeutic response dictates (D'Esopo, 1963).

Gerszten *et al.* (1963) found that 56 per cent of tuberculosis patients admitted to sanitoriums in the United States had organisms that were susceptible to the three drugs streptomycin, INH, and PAS. These patients had no prior history of drug therapy. Of patients who gave a prior history of drug treatment for their tuberculosis, only 33 per cent had organisms sensitive to all three drugs. The matter is extremely complicated because many patients who, on admission, harbored tuberculosis organisms that were resistant to the three drugs did recover as a result of intensive therapy.

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# 12

# *The Chemotherapy of Tropical Diseases*

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An arbitrary classification of diseases has been followed in the text in order to present most cogently the aspects of chemotherapy of the infectious diseases. The selections have been made partly by drug classes and partly by disease entities. In this way the pharmacologic principles involved in chemotherapy may be illustrated. The drugs appraised in this chapter act systemically in the prevention and treatment of microbial, parasitic, protozoal, and fungal infections. Helminthiasis and amebiasis, so closely allied to the tropical infectious diseases, are reviewed in the following chapters.

Special attention is given to malaria, perhaps because we have had such striking success in conquering this disease. This should not imply that many of the tropical and semi-tropical diseases which are subsequently considered very briefly are not medically significant. The fact is that we do not have curative drugs for most of these diseases. As will be pointed out, former classifications of diseases as "tropical diseases" are no longer suitably descriptive. The rapid mobility of people in the world today makes these classifications meaningless. Indeed, the diagnosis of a case of falciparum malaria in New York City in 1963 illustrates this point. The patient had recently returned from a vacation in Haiti, and the initial diagnosis was atypical viral pneumonia.

The first significant success with synthetic drugs in chemotherapy was the discovery of the value of sodium arsanilate, or atoxyl, in the treatment of African sleeping sickness. This finding encouraged Paul Ehrlich to pursue his work with the organic arsenicals. In the past 50 years many noteworthy drugs useful in a number of tropical diseases have been discovered. These drugs, if they are not antibiotics, are considered in this chapter.

## CHEMOTHERAPY OF MALARIA

In the history of chemotherapy of infectious diseases, quinine and malaria occupy a special place. Cinchona bark, perhaps the first specific drug, was introduced into Europe as a febrifuge following the Spanish conquests of South America. Quinine, the chief alkaloid of the native South American cinchona tree, was isolated from the crude bark in 1820. In succeeding decades the Netherlands Indies, with their cinchona plantations, acquired a virtual monopoly of the industry and of the production of quinine. During World War II this region was lost to the Allied Powers. As a result, a major chemical research program was established that led to the synthesis of superior antimalarial drugs.

Malaria is one of the most prevalent of all human infectious diseases. This incapacitating infection has a wide geographic distribution, exacts a staggering toll of human life, and maintains a check on the economic progress of a community. In 1950 it was estimated that 300 million people were afflicted with malaria and that approximately 3 million persons died of malaria annually. As a result of international efforts to control Anopheles mosquitoes and the widespread use of effective antimalarial drugs, deaths from malaria dropped to about 1 million people in 1957, and more than 50 million people in 9 countries, living in what were formerly malarious areas, have now been fully protected. The World Health Organization has predicted that it may be possible to provide similar protection to 550 million more people by 1965.

Malaria as an endemic disease has been completely eradicated from the United States. In Mexico, Brazil, Argentina, and all the other countries of the Americas with the exception of Cuba, malaria eradication is progressing rapidly.

In parts of Greece, Italy, Turkey, and Yugoslavia, countries where malaria was a serious post-World War II problem, the disease has almost disappeared. Indeed recent developments in malaria control under the aegis of the World Health Organization have made possible the daring concept that malaria can be eradicated from most areas of the world. Systematic control measures, involving the use of insecticides and drug therapy, have proved that a vigorous 3-year program will result in the eradication of the parasite even though the mosquito vector may persist. Thus today it may be possible to achieve complete control of the disease even though malaria may have been endemic in a region for centuries.

By 1963 it had become apparent that contrary to the experience of the preceding 20 years malaria parasites were developing tolerance to the antimalarial drugs. Lessened sensitivity of some strains of *P. falciparum* was first observed in 1952 against chlorguanide. In succeeding years these reports increased, and pyrimethamine resistance was encountered in *P. vivax* and *P. falciparum*. A strain of *P. falciparum* was discovered in a patient with a high degree of tolerance to chloroquine. This strain was also resistant to amodiaquin and hydroxychloroquine. Chloroquine-resistant falciparum malaria has been found in Brazil, Colombia, Venezuela, Viet Nam, and Thailand. A single instance of relapsing vivax malaria has been found to be resistant to primaquine. Thus an all too familiar pattern of drug-resistant organisms may be emerging. Chloroquine-resistant strains of falciparum malaria are also resistant to other drugs, with the exception of quinine, and for this reason the search for better antimalarials must go on. It appears that the great cooperative effort between nations must continue without respite to provide the long-sought goal of malaria eradication.

### Nature of malaria.

Malaria is a febrile disease. It is most prevalent in tropical regions that favor the propagation of mosquitoes and the development of the sexual cycle of the parasite within the body of these insects.

Malaria as a disease can be considered from 3 aspects:

1. The vector, the mosquito
2. The parasite, the plasmodium
3. The clinical symptoms in man

The symptoms of malaria are produced by the development of the parasite within the body of the patient. These symptoms are related to the type of malaria and the cycle of the entrance, growth, division, and release of the merozoites in red blood cells. The clinical symptoms in man are discussed in the consideration of the behavior of the parasites of the several types of malaria.

**The vector.** Human malaria is transmitted only by Anopheles mosquitoes. About 350 species of anophelines have been described, but only 180 are said to be capable of transmitting malaria. Nearly 60 species are known to transmit the disease under *natural conditions;* however, only a few are important vectors. To be an *effective* carrier of the disease, the species of mosquito must be present in large numbers in the malarious region, it must frequent human habitation, and climatic conditions must favor the development of the sexual cycle of the plasmodium within the mosquito.

An understanding of these factors clarifies the clinical disease which we ordinarily call "malaria". There are different vector species as well as different types of parasites harbored by the mosquito. In retrospect, it is little wonder the early investigators labored so long and painfully to unravel the thread of the mystery of malaria. Indeed, it was not until 1898 that Ronald Ross proved that the parasite was transmitted by mosquitoes.

Only the female mosquito sucks blood, and hence only the female is concerned in the transmission of the disease. The parasites from plasmodia-infested blood undergo sexual reproduction within the body of the mosquito. This is the insect phase.

It has been possible to control malaria in certain regions by the use of insecticides. The most favorable malaria control has been achieved by combined use of chemotherapeutic agents and insecticides. The addition of antimalarial drugs to cooking salt has been found to shorten the time necessary for the elimination of residual malaria, which, owing to certain forms of transmission, may persist in some regions for years.

Malariologists are enthusiastic regarding the future of malaria vector control by insecticidal chemicals, in spite of the development of resistance to DDT by a variety of arthopods. These insects have developed not only a physiologic resistance to the toxic spray but have also changed their habits of behavior to avoid contact with areas where the insecticides are sprayed. Residual fumigants are known, such as malathion vapor, which are nearly 100 per cent lethal to mosquitoes in the general vicinity of a sprayed area for 1 month after an application. The newly developed mosquito control technic of the slow release of an insecticidal vapor over a long period of time (3 to 4 months) has many advantages. A container containing the volatile insecticide is simply located in the general region to be protected. This will be lethal to the insects for a protracted period of time. This insecticide is DDVP (O,O-dimethyl-2,2-dichlorovinyl phosphate) in a solid formulation (Mathis *et al.*, 1961). This device may offer a solution to many of the problems of vector control. In addition, the necessity for public health measures that control all insects that bite man is evident. It is argued that these insects constitute a public nuisance even though they may not be directly involved in disease transmission. This is in accord with the view that good health requires sewage disposal because sewage is objectionable in addition to its disease potential, clean water because it is esthetically acceptable, and smog-free air because it has a positive public health attribute.

**The parasite.** The parasite of malaria is a

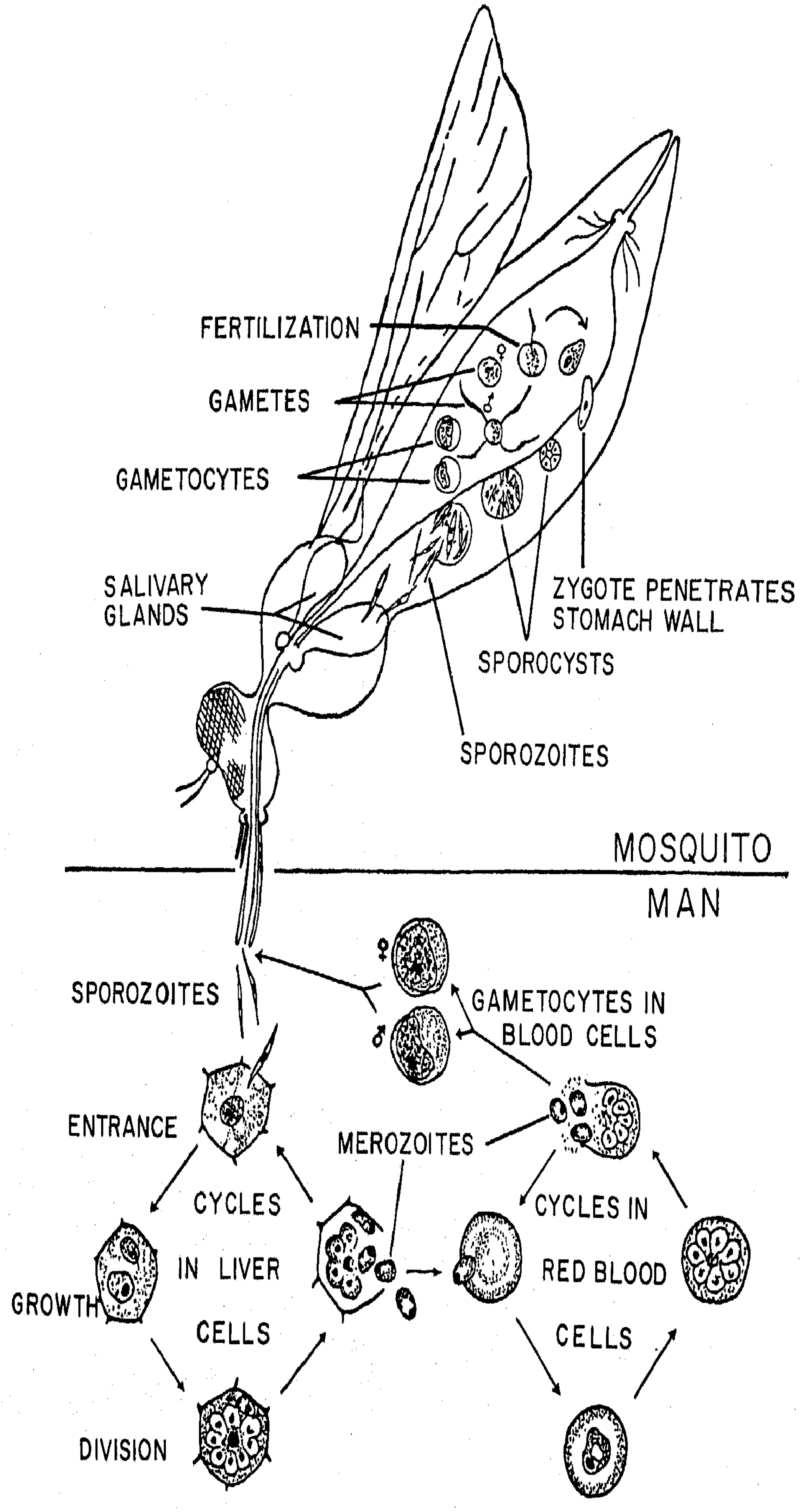


FIG. 12-1. Life history of *Plasmodium vivax* in the mosquito and man. Asexual cycles take place in the human body, in cells of the liver and in red blood cells. The cycle in the blood is completed every two days, causing chills and fever in the patient at two-day intervals. The sexual cycle in *Anopheles* requires about twelve days. (From Kenoyer, Goddard and Miller, General Biology, Third Ed., Harper Brothers, 1953.)

protozoan of the genus *Plasmodium*. In man, 4 species of plasmodia are known to cause malaria. These are really 4 diseases, but only 2 are of importance—*malignant tertian malaria* and *benign tertian malaria*. The different types of malaria and the causative plasmodia are as follows:

1. Malignant tertian malaria—*Plasmodium falciparum*
2. Benign tertian malaria—*Plasmodium vivax*
3. Quartan malaria—*Plasmodium malariae*
4. A rare type of malaria—*Plasmodium ovale*

Each species of *Plasmodium* will include a number of different *strains*. They look alike microscopically but their virulence differs. Some are very resistant to the antimalarial drugs; other strains of the same species will be more easily destroyed. It is not known whether these resistant strains exist as mutants of more resistant forms or whether they have developed an adaptive defense mechanism as a strain characteristic. The important fact remains that not all strains of the malaria parasite will be equally amenable to chemotherapy.

The life cycle of the plasmodium occurs in 2 phases, one in the Anopheles mosquito and the other in man. The sexual cycle of development of the plasmodium takes place in the mosquito. After the insect bites a malarious subject harboring gametocytes in his blood, from 7 to 10 days are required before the mosquito is infective for man. After the mosquito sucks blood containing gametocytes, or the sexual form of the parasite, fertilization of the female gametocyte by the male takes place in the insect's body. The fertilized form penetrates the stomach wall and matures its sporozoites, which are liberated to become embedded in the salivary glands of the insect, ready to transmit the disease to another human at the time of a subsequent bite. In this way the infected mosquito can inject man with an infectious dose of the plasmodium as sporozoites.

The fate of the sporozoites of malaria when they are deposited by a mosquito in a nonsusceptible host is not known. For example, *P. gallinaceum* will be infectious for chicks when bitten by infected *Aedes aegypti* mosquitoes but will not be transmitted to mice when these animals are bitten by the same mosquitoes. Sporozoites are not destroyed *in vitro* in the drawn blood of a susceptible host, but they disappear quickly from the blood and tissues of a nonsusceptible animal when bitten by a mosquito (Beckman, 1963). A clue to the mystery of the natural protection to malaria may be found in some animal species and man by uncovering the nature of a factor in the skin. Indeed, the long-sought integument-deposited insect repellant, a chemical that could be taken by mouth and deposited in the skin, might be discovered by knowledge of the "active principle" of the skin of the nonsusceptible host.

In man the sporozoites from the mosquito go through a series of stages in the blood and tissues. It is now accepted that the early development of sporozoite-induced malaria in man takes place in fixed-tissue cells. Further, it is believed that persistent tissue forms, *exoerythrocytic forms*, are responsible for the repeated relapses of vivax malaria infections. Such persistent tissue forms do not occur in falciparum infections.

The symptoms of malaria are associated with the multiplication and development of the merozoites in the blood erythrocytes. The period of incubation in man from the time of introduction of sporozoites by the mosquito bite to the appearance of the first clinical symptoms is approximately 10 days for vivax and falciparum malaria.

The erythrocytic form of the parasite undergoes segmentation after a period of growth. From 15 to 20 spores, or *merozoites*, are evolved from each organism. The merozoite within the red blood cell swells and becomes vacuolated. Eventually the red cell ruptures, setting the merozoites free in the circulating blood. They enter other red blood cells and the process is repeated. When the population of organisms increases to such an extent that a large number of red blood cells are involved, symptoms appear.

The asexual cycle in the blood consists of trophozoites from the mosquito-induced sporozoites, which give rise to schizonts after nuclear division within the red blood cell. The schizonts break up into a number of merozoites. Some merozoites give rise to sexual forms, the gametocytes; other merozoites enter the red blood cells to continue to develop and cause subsequent attacks of fever.

After the infection has become well established and the patient has suffered a number of malarial attacks, gametocytes may be found in his blood. These sexual forms cause no symptoms. The male and female gametocytes float harmlessly in the circulating blood and are transmissible to a susceptible mosquito when the individual is bitten. Why certain merozoites give rise to the sexual forms is not known. However, certain antimalarial drugs so affect the plasmodium in man that the gametocytes fail to undergo reproduction after transmission to the mosquito.

In *vivax malaria* the time of entrance of the parasite into the red blood cell and the subsequent destruction of the cell is typically 48 hours. The term "tertian malaria" applied to vivax refers to the sequence of attacks correlated with this cycle. In *quartan malaria* approximately 72 hours is required for the cycle. In *estivo-autumnal* or *falciparum malaria* the interval is irregular, and fever may be continuous or malignant.

The paroxysms of chills, fever, and sweating in malaria are related to the release of the sporulating organisms from the red cells. The accumulated toxins and malarial pigment are released into the circulation. The specific hemolytic toxin destroys an additional number of red blood cells.

There are a number of factors that permit a differentiation of *P. vivax* malaria and *P. falciparum* malaria. Strains of each of these species act dissimilarly, having different clinical characteristics causing diverse chemotherapeutic problems. In fact one of the great difficulties in testing antimalarial drugs is the establishment of a standard strain. In experimental studies the *Chesson*, *Madagascar*, and *St. Elizabeth* strains of *P. vivax* have been employed.

The disease *falciparum malaria* (*malignant tertian malaria*) is a fulminating infection which, without drug therapy, may progress rapidly to a fatal termination. However, by the use of proper antimalarials, the infection may be promptly cured. *Falciparum malaria does not produce persisting tissue parasites, as does vivax malaria.* This disease has little or no tendency to relapse after drug therapy because all the exoerythrocytic forms are converted to blood stages with the onset of the erythrocytic phase. Falciparum malaria has a high mortality rate in susceptible individuals, if recognized late or treated inadequately. Malignant tertian malaria may present variable clinical manifestations.

*Vivax malaria* (*benign tertian malaria*) is more complex than falciparum malaria. This disease is not prone to progress rapidly to a fatal termination. Its most characteristic features are its delayed primary attack, long duration, and tendency to relapse, which usually occurs 6 to 12 months after infection. In vivax malaria the tissue parasites have the ability to persist for long periods. The tissue forms appear to be capable of releasing new lines of erythrocytic forms at periodic intervals. These give rise to recurrent attacks and clinical relapses. The attack may be suppressed by drug therapy, but if the drug is discontinued, new erythrocytic forms emerge from the persisting tissue forms and another relapse occurs.

If vivax malaria is initiated in man experimentally by the transfer of infected blood, no tissue stages of the parasite are formed. The recipient may become acutely ill with malaria, but no relapses will occur after suppressive treatment. Thus to study the curative value of an antimalarial, mosquito-induced infections must be employed.

### Malaria strain differences.

Since 1942 the studies of Coatney *et al.* (1948, 1958, 1963) and of Alving and associates (1947, 1960) in the United States, Fairley in Australia, and other workers, have revealed the marked differences in *strains of vivax malaria*. The tendency to chronicity, so characteristic of vivax malaria, is related to the development of late exoerythrocyte forms of the parasite. Each strain has a characteristic relapse pattern that depends upon the persistence of the fixed-tissue cell forms. A strain of vivax parasites known as the Chesson strain is used for the drug screening of antimalarials in human volunteers. This method of evaluating antimalarial drugs on purposefully infected human volunteers has become a standard procedure.

## THE SYNTHETIC ANTIMALARIAL DRUGS

Under the duress of wartime emergency, in 1940 to 1945, many notable contributions were made in the discovery of superior antimalarial drugs. The skill of the organic chemist in preparing more effective drugs was demonstrated before the war, however, by the synthesis of quinacrine and pamaquine. These drugs pointed the way to the discovery of a number of excellent antimalarials.

### Categories of antimalarial activity.

Drugs used in the treatment, prevention, and cure of malaria fall into one or more of the following categories:

1. *Prophylactic:* a drug possessing activity against the mosquito-introduced sporozoites or the parasites of the primary fixed-tissue phase of the disease.
2. *Suppressive:* a drug possessing activity against the asexual erythrocytic forms of the parasite.
3. *Curative:* a drug possessing activity against the persisting tissue parasites so characteristic of vivax malaria.
4. *Gametocidal:* a drug possessing activity against the gametocytes or sexual forms of the parasite.

*Clinical cure* may be achieved by the use of a suppressive drug. In this case symptomatic relief is obtained promptly, but relapse may occur.

*Radical cure* may result from chemotherapy. In this instance symptomatic relief is obtained in addition to the complete eradication of secondary parasites, so that relapse cannot occur.

Quinine is a suppressive drug but a poor one for the control of vivax malaria. The use of quinacrine by the Allied armies represented a great advantage. It led to the practical abolition of clinical attacks of malaria under fighting conditions, though over 400,000 American troops were infected with vivax malaria, which recurred as soon as the drug was stopped. It abolished malignant tertian malaria as a clinical problem both during and after the war; and finally, it reduced the death rate from malaria to less than 1 per 2000 men having the disease.

As effective as quinacrine was, there was a need for drugs possessing both prophylactic and curative virtues. *Chloroquine*, *primaquine*, and *pyrimethamine* emerged from studies of many thousands of compounds as drugs offering superior antimalarial properties. Table 12-1 lists the important antimalarial drugs.

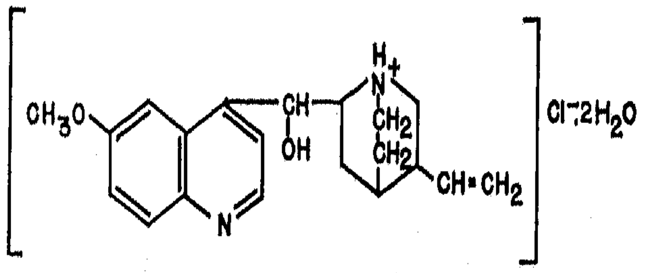
TABLE 12-1

*A Table of Antimalarial Drugs*

Cinchona derivative
  quinine
Acridine derivative
  quinacrine (Atabrine)
4-Aminoquinoline derivatives
  chloroquine (Aralen)
  hydroxychloroquine (Plaquenil)
  amodiaquin (Camoquin)
8-Aminoquinoline derivatives
pamaquine (Plasmochin)
  pentaquine
  primaquine
Biguanide derivative
  chlorguanide (Paludrine)
Diaminopyrimidine derivative
  pyrimethamine (Daraprim)

## CHEMISTRY OF THE ANTIMALARIAL DRUGS

The alkaloids of cinchona are quinoline derivatives. Cinchonine, which may be considered as the parent substance, consists of a *quinoline heterocycle* and a *quinuclidine heterocycle* joined through a *secondary alcohol* group.



Quinine Hydrochloride, N.F.

The removal of the vinyl group or the methoxy group in the quinine molecule does not influence its antimalarial activity. The secondary alcohol group is essential for activity.

In 1891 Ehrlich showed that methylene blue exhibited some antimalarial activity, although less marked than that of quinine. No substantial advance was made in the treatment of this disease until 1926, when Schülemann *et al.* began their studies on modifications of the methylene blue molecule, and eventually succeeded in preparing pamaquine (Plasmochin). This compound contains the quinoline ring also present in quinine. However, clinical investigations showed that pamaquine, though a much more destructive agent against the gametocytes than quinine, was less effective against the trophozoites. An extension of these studies led to the development of quinacrine in 1930. Quinacrine is an acridine derivative only remotely related to quinine chemically.

In the search for suppressive drugs superior to quinacrine during World War II, the 4-aminoquinolines were investigated in the United States. As a result, *chloroquine* and *amodiaquin* were discovered. In Great Britain a study of the biguanides produced the antimalarial *chlorguanide*.

By 1948 it became evident that suppressive drug therapy would not reduce the relapse rate in vivax malaria even in maximal tolerated doses of the drugs then available. Attention was refocused upon the only known drug having curative properties, namely, pamaquine. Accordingly, the 8-aminoquinolines were studied. Drugs of this class were discovered to be gametocidal but relatively toxic. Pentaquine and primaquine were found to be the most satisfactory and the least toxic and, combined with quinine therapy, gave radical cure of vivax malaria. However, there were many disadvantages of the 8-aminoquinolines, and the search was pursued further.

A new class of antimalarial drugs, the *diaminopyrimidines*, evolved from the fundamental studies of Hitchings and his associates (1960) on the role of nucleic acids in cell multiplication. These studies were undertaken on the theory that the requirements for the precursors of nucleic acids by parasites must in general be greater than those of the host. It was assumed that the more rapid cell division and hence the greater nucleic acid synthesis by the parasite would make this point of attack most vulnerable. In extensive investigations it was learned that the 2,4-diaminopyrimidines possessed an antagonistic effect upon nucleic acid synthesis. This was true for various species of organisms and for the cells of mammalian tissues. The 2,4-diaminopyrimidines were found to antagonize folic acid in much the same way the 4-aminofolic acids do, but the pyrimidines are highly selective in their action. Pyrimethamine (Daraprim) evolved from this study as a type of structural analog of folinic acid that was adapted to the displacement of this metabolite from its *apoenzyme* in the malaria plasmodia. Thus it may be considered to be an antimetabolite. Pyrimethamine, like aminopterin, is an irreversible inhibitor of folic acid reductase according to the concept of antimetabolites proposed by Baker (1959).

Pyrimethamine proved to be an effective suppressive antimalarial. In addition, it has been shown to prevent the development of gametocytes in the mosquito and thus is capable of interrupting the malarial cycle. These facts, together with the small dose and low toxicity, make pyrimethamine one of the most promising of the antimalarial drugs. It would obviously be a great advantage to have a drug which in a single dose would effect radical cure of any malarial infection without risk, while at the same time the presence of the drug in the circulating blood would prevent mosquito transmission. Indeed, based upon recent developments in the chemotherapy of malaria, it is possible that this ideal will be achieved.

### Antimalarial drugs with prolonged actions.

The possibilities of prolonging the duration of action of antimalarial drugs have attracted the attention of malariologists for many years. To interrupt the transmission of malaria by drug therapy, it is necessary to maintain an effective schizontocidal concentration of the drug in the blood of every individual in the community. This requirement poses dosage difficulties unless the drug has a long persistence in the body. Experience has shown that it is generally not possible to persuade people to take drugs regularly and frequently for a prolonged time. It would be a distinct advantage if a drug could be discovered that would maintain an effective blood level for a month or longer after a single oral dose. The usual technics to prolong drug action, *e.g.*, delayed absorption or excretion, have not proved fruitful in prolonging antimalarial effects. Recently, a new approach has been devised based upon the synthesis of a slowly absorbed, high molecular weight salt, a metabolite of chlorguanide. This drug is injected intramuscularly and is released slowly from the tissue depot for many months. The early clinical experiences with this agent, known as chlorguanide triazine pamoate, are described on page 153.

### Metabolites of antimalarial drugs.

The discovery of superior antimalarial drugs must be based on an understanding of the metabolism and biochemistry of the malarial parasites. However, studies conducted during the past 25

years employing the approaches fruitful in other areas of chemotherapy have not been very successful. Antimalarials have been studied as growth factor antagonists, enzyme inhibitors, and as competitors for protein synthesis by the plasmodium. In 1945 the antimalarial chlorguanide was synthesized on the basis of purely chemical reasoning. It was proposed to possess structural similarities to riboflavin and decomposition products of the pyrimidine nucleus (Curd, Davey, and Rose, 1945). The drug subsequently was shown to be unaffected by added riboflavin *in vitro*. Indeed, chlorguanide is essentially inactive *per se*, and a triazine metabolite was discovered to be the active form in the body. The therapeutic advantages of a long-acting form of this metabolite of chlorguanide have renewed interest in the metabolic degradation products of the antimalarial drugs.

### Other Pharmacologic Actions of the Antimalarial Drugs

In addition to their usefulness in the treatment of malaria and the contribution which the discovery of these drugs has made to an understanding of the enzymic processes of drug action, the antimalarial agents have proved to have varied pharmacologic effects.

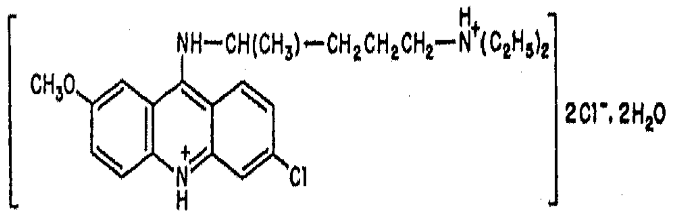
In the following sections reference is made to their use in certain forms of lupus erythematosus, rheumatoid arthritis, amebiasis, and as anthelmintics. An unusual effect of quinacrine, chloroquine, hydroxychloroquine, and amodiaquin is to increase the skin's tolerance to ultraviolet light of a specific spectral range of 2900 to 3100 Å. The mechanism of action in this regard is unknown except that these drugs do not act as light barriers in the skin. Certain of the antimalarial drugs are effective in treating the symptoms of polymorphous light eruptions (Shaffer *et al.*, 1959). The extensive literature on this subject cannot be reviewed, but the interested student may read the references cited. One fascinating aspect of the potential use of these drugs is in radiation protection in radioactive laboratory operations and the protection of man in space flight against harmful radiations.

Recent reports have described the use of hydroxychloroquine in the treatment of patients with "sludging" and various vascular diseases. Chloroquine has produced dramatic improvement in a few cases of infectious mononucleosis. These clinical findings suggest that the antimalarial agents have multifaceted therapeutic uses.

### Acridine Derivative

**Quinacrine Hydrochloride, U.S.P. (Atabrine)** is a yellow, bitter, crystalline powder, soluble in water to the extent of 3 per cent. Its solutions are slightly acid in reaction. Like quinine, quinacrine solutions are fluorescent. It is an acridine dye and structurally not related to quinine. It is 2-chloro-7-methoxy-5-(1-methyl-4-diethylaminobutylamino)-acridine dihydrochloride dihydrate.

Quinacrine is quickly absorbed from the gastrointestinal tract; it is slowly excreted. Only very low plasma concentrations are achieved after a 0.1-gm. daily dose during the first 2 to 3 days of therapy because the drug is localized and concentrated in the tissues. For this reason large doses are given early in malaria therapy. Studies on the distribution of quinacrine in experimental animals indicate that the drug may reach concentrations 10,000 to 20,000 times greater in the liver and spleen than in the blood plasma. After several days' administration there may be a yellow discoloration of the skin as a result of the deposition of an acridine pigment.



Quinacrine Hydrochloride, U.S.P.

**Administration.** The principal action of quinacrine is against the asexual erythrocytic parasites. When adequate dosage is given, the drug stops the acute attack of malaria. Persistent exoerythrocytic forms of *P. vivax* are not affected, and therefore vivax malaria will relapse 4 to 6 weeks after treatment.

When employed protectively, quinacrine has no activity against mosquito-induced sporozoites and hence has no causative prophylactic action. It effectively suppresses erythrocytic forms, however, and if dosage is continued for a sufficient time (4 weeks) after exposure, the drug will prevent falciparum malaria.

The recommended adult antimalarial dosage is 0.2 gm. with 1 gm. of sodium bicarbonate by mouth with from 200 to 300 ml. of water or other fluid every 6 hours for 5 doses, followed by 0.1 gm. 3 times a day after meals for 6 days. A suppressive dose is 0.1 gm. daily.

**Toxicity.** In the treatment of malaria the number of untoward reactions following the oral administration of doses up to 0.7 gm./week has been comparatively small. Nausea and unpleasant reactions of a minor nature usually disappear within a few days if the drug administration is continued.

Cutaneous toxic reactions, though rare, have been observed. The symptoms are a lichenoid and eczematoid dermatitis with a secondary exfoliative dermatitis. True hypersensitivity to quinacrine has been observed. Such hypersensitive persons develop an aplastic anemia, agranulocytosis, and hepatitis along with the cutaneous symptoms. Fortunately such reactions are rare, but the fatality rate has been almost 100 per cent. More undesirable reactions occur with quinacrine therapy than accompany treatment with the 4-aminoquinolines.

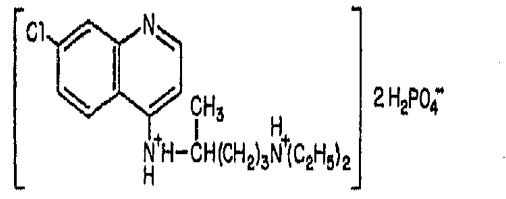
**Other therapeutic uses.** Quinacrine has been found to be effective in producing remissions of the disease *lupus erythematosus*. However, chloroquine is considerably less toxic and is considered superior to quinacrine in this disease. Quinacrine has also been used in the treatment of rheumatoid arthritis. A description of the use of the antimalarial drugs in these diseases is given on page 844.

Quinacrine possesses anthelmintic properties and is the drug of choice in tapeworm infestation (see page 191).

### 4-Aminoquinoline Derivatives

**Chloroquine Phosphate, U.S.P.** (Aralen) is a white, crystalline powder readily soluble in water. Chloroquine is 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline.

Chloroquine has been found to be a highly effective and relatively well-tolerated antimalarial. It is active against erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent vivax infection when used prophylactically, nor does it prevent relapses in vivax malaria. The drug is most useful in *P. vivax* malaria as a suppressive agent and in the treatment of the acute attacks. In this respect chloroquine is significantly superior to quinacrine or quinine. In falciparum malaria it abolishes the acute attack and brings about a complete cure of the infection.



Chloroquine Phosphate, U.S.P.

At present the recommended treatment for vivax malaria is chloroquine as a suppressive drug for persons living in a malarious area. Immediately after leaving the region, primaquine should be taken for 14 days to eradicate the persisting tissue forms of the parasite.

Chloroquine is almost completely absorbed from the gastrointestinal tract. It is absorbed more rapidly than quinacrine, but its fate and excretion are similar to quinacrine and the related 4-aminoquinolines. It is deposited in the liver, spleen, kidneys, lungs, and leukocytes. Relatively less is found in the central nervous system. Approximately 50 per cent of the drug in the plasma is in a bound form. It is very slowly excreted in the urine as the free drug and as the de-ethylated secondary amine. In rats chronic administration of chloroquine produces a marked concentration of the drug in the iris and choroid of the eye. Its concentration in human ocular tissue has not been reported. The tendency to concentrate in the eye tissue may account for the eye pathology observed after long-term therapy with the drug. This toxic effect is not associated with its antimalarial use.

For 10 years chloroquine proved to be one of the most dependable antimalarials for the treatment of the acute clinical attacks of vivax malaria and the cure of falciparum malaria. The discovery of a strain of chloroquine-resistant *P. falciparum* in Colombia, South America, in 1961, and subsequent similar observations in other countries, proved to be a serious development (Powell *et al.*, 1963). It is obvious that the problem of drug resistance to the antimalarials, although infrequent at present, is of fundamental concern for the future. It is evident that cases of alleged "drug resistance" must be fully investigated. Presumed drug failures may be reported when in fact the drug was not actually taken by the patient.

**Administration.** The drug causes an abrupt termination of the clinical attack of vivax malaria and produces a radical cure of falciparum malaria when administered for only 3 days. It is administered by mouth in 0.25-gm. tablets. In the treatment of the acute attack an initial dose of 1 gm. is given. This is followed by an additional dose of 0.5 gm. 6 to 8 hours later. A dose of 0.5 gm. given on 2 consecutive days thereafter usually is sufficient to cause the disappearance of symptoms. A small suppressive dose of 0.5 gm. weekly will effectively suppress vivax malaria. This regimen eradicates infections caused by *P. falciparum*.

**Other therapeutic uses.** Chloroquine is a useful drug in amebiasis (see page 177). The value of this antimalarial in chronic discoid lupus erythematosus is now generally accepted; its status in the disseminated or systemic form of the disease is controversial. Chloroquine phosphate frequently produces some symptomatic relief in rheumatoid arthritis (see page 844).

Chloroquine and hydroxychloroquine have been used in the treatment of cardiac arrhythmias (see page 656). According to Hess and Schmidt (1959), chloroquine and quinidine are equally effective in decreasing the resting excitability of isolated cat papillary muscle. Chloroquine is capable of terminating experimental atrial fibrillation in dogs.

**Toxicity.** The acute toxicity of chloroquine for experimental animals is about the same as that of quinacrine.

In man, following the administration of doses adequate for treatment of malaria, symptoms of mild and transient headache, visual disturbances, pruritis, and gastrointestinal complaints have been reported. In overdosage the drug has produced blurring of vision, inability to focus the eyes rapidly, dizziness, insomnia, and occasionally skin lesions and pruritis. It is generally agreed that side effects are seldom observed when chloroquine is used in the recommended dosage as an antimalarial.

With the recent use of chloroquine in rheumatoid arthritis and lupus erythematosus, this drug has been administered in high doses (0.25 gm./day or more) for as long as 5 years. A number of reports have described corneal, retinal, and visual changes after chloroquine therapy. Hobbs *et al.* (1959) observed apparent irreversible visual damage in 3 patients with macular lesions and narrowed retinal vessels. These patients had received chloroquine for 3 to 5 years. The retinopathy may be an idiosyncratic response, for only a few such cases have been found. Other workers have described opacities of the corneal epithelium in similar patients, although these were reversible after withdrawal of the drug. Some subjects experience a "halo" or blurring of naked lights when viewing these lights after prolonged chloroquine therapy. Yellow hyperpigmentation, graying, or bleaching of the hair has also been described.

Acute toxicity from chloroquine has produced several deaths. Pille *et al.* (1959) described a suicide where the estimated dose was 100 mg. of chloroquine base per kg., which is approximately 5 times the toxic limit. Death ensued within 2.5 hours from respiratory failure. Fatalities in young children have been reported: a 14-month-old boy died after ingestion of 1 to 2 gm., a 2-year-old boy after less than 3.4 gm., and a 3-year-old boy after less than 1 gm. The notable feature of these deaths is the rapidity with which death occurred, all within 2.5 hours. Respiratory and cardiac arrest was produced suddenly. The rapid fatality is explained by complete and prompt absorption of the drug from the gastrointestinal tract, resulting in high blood concentrations and depression of vasomotor function and respiration. Prompt emptying of the stomach following ingestion of toxic amounts of the drug is imperative.

When chloroquine phosphate is employed in relatively high doses for many months in the treatment of rheumatoid arthritis, in addition to the side effects described, serious skin reactions may be manifested. These include dryness, itching, urticaria, maculopapular eruption, desquamation, exfoliation, increased pigmentation, and alopecia. Exposure to direct sun or ultraviolet light may aggravate the dermatitis. In the light of the possible serious toxic effects of chloroquine in the doses employed in diseases other than the malarias, patients receiving this drug should have periodic blood cell counts.

**Hydroxychloroquine Sulfate, U.S.P. (Plaquenil)** is chemically similar to chloroquine with the exception that a hydroxyethyl group has been substituted for an ethyl group on the tertiary amino nitrogen. Hydroxychloroquine is 7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino]-quinoline. The sulfate is a colorless, crystalline solid, soluble in water.

Hydroxychloroquine was introduced as an antimalarial drug having a high degree of clinical safety and effectiveness. Perhaps its outstanding uses have been in the treatment of rheumatoid arthritis, chronic discoid lupus erythematosus, and light-sensitivity eruptions. The use of this drug in the treatment of various vascular diseases as a "de-sludging" agent is of interest.

Hydroxychloroquine is better tolerated than chloroquine in most patients, although there is marked variation in the degree of individual patient tolerance to hydroxychloroquine, chloroquine and quinacrine. The incidence of side effects is lower with hydroxychloroquine therapy than with chloroquine therapy, but the reactions are similar and may be equally severe. A suicidal fatality followed the ingestion of 54 or more 200-mg. tablets of hydroxychloroquine.

In the treatment of falciparum malaria a single 800-mg. dose of hydroxychloroquine sulfate has been used to eradicate the infection and to terminate acute attacks of *P. vivax* malaria. The suppressive dose for vivax malaria is 400 mg. weekly. A total dose of 2.0 gm. (equivalent to 1.5 gm. of the base) given over a period of 3 days is the usual course of treatment.

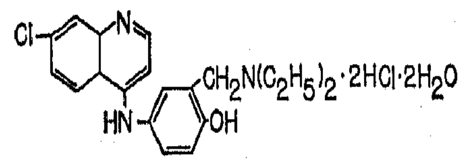
In *rheumatoid arthritis* hydroxychloroquine sulfate is administered orally in doses of 400 to 600 mg. daily. The dose is usually divided into 200-mg. tablets 2 to 3 times daily. The drug has a cumulative action, and several weeks of medication are required for beneficial therapeutic effects in rheumatoid arthritis. Side effects may occur early and resemble those of chloroquine therapy. There is great individual variation in patient response. A number of clinical reports stress the advantages of hydroxychloroquine over chloroquine (Scherbel, 1958).

Madow (1960) used doses of 200 mg. 4 times a day for 1 week, followed by 200-mg. maintenance doses 3 times a day of hydroxychloroquine sulfate in treating patients with coronary artery disease, cerebral vascular disease, and intermittent claudication. These patients had observable changes in the circulation seen in the bulbar conjunctiva, with the presence of aggregates in the peripheral circulation that tended to reduce the flow. The phenomenon is described as "sludging." Hydroxychloroquine was found to be an effective "de-sludging agent" and produced beneficial responses in many patients. The mechanism of action in this condition is unknown.

A combination of 25 mg. of quinacrine hydrochloride, 65 mg. of chloroquine phosphate, and 50 mg. of hydroxychloroquine sulfate, called Triquin, has been used in light-sensitivity eruption therapy and in lupus erythematosus. Tye and associates (1959), in a report typical of several publications, found this combination of drugs more efficacious in some patients at certain times during the course of treating chronic discoid lupus erythematosus than any single drug. Some individuals can tolerate the three-drug combination but are intolerant to chloroquine or quinacrine when these drugs are administered alone in the treatment of discoid lupus erythematosus.

The initial adult dose is 1 to 2 tablets orally 4 times a day. Each Triquin tablet contains the dose of the combination of drugs stated previously. With improvement, dosage may be gradually reduced to 1 to 2 tablets daily. The usual precautions of antimalarial therapy are observed.

**Amodiaquine Hydrochloride, U.S.P. (Camoquin)** as the dihydrate is a light yellow, crystalline powder. It is soluble in water to the extent of 5 per cent. Amodiaquine is 4-(3'-diethylaminomethyl-4'-hydroxyanilino)-7-chloroquinoline.



Amodiaquine Hydrochloride, U.S.P.

Amodiaquine produces a rapid suppression of all types of malaria and appears to be an excellent drug for treating clinical symptoms of malaria. The drug is closely related to chloroquine, and its effectiveness in malaria is similar to this 4-aminoquinoline. Amodiaquine is apparently effective in a single adult therapeutic dose.

Amodiaquine is rapidly absorbed from the gastrointestinal tract, and adequate blood concentrations are achieved 1 hour after oral administration. In animals the drug is unequally distributed in body tissues. It is concentrated in the liver and the kidneys, with the highest

amount found in the spleen. The drug is slowly excreted, and small amounts remain in the tissues for a week or more after a single dose. Between 10 and 20 per cent of the daily dose of amodiaquine is excreted in the urine. The drug is not excreted in the urine in an unmodified form. Excretion can be enhanced by the oral administration of ammonium chloride.

**Administration.** As an antimalarial the drug is administered orally in the form of tablets. The adult dose is three 0.2-gm. tablets taken as a single dose. The results obtained by various workers indicate that a single dose produces a more favorable response than even larger doses when administered in divided amounts. Since the toxicity of the drug is low, larger doses may be given with safety to normal adults. For example, doses of 0.4 gm. 3 times a day for a period of 5 days have been administered in special circumstances. The single dose regimen available in the case of amodiaquine makes it advantageous for tropical native populations, where it is difficult to maintain long dosage schedules.

Amodiaquine produces a rapid suppression and cure of falciparum malaria. Like chloroquine, it is a suppressive but not a cure for vivax malaria. Its rapidity of action in controlling the clinical attack of malaria compares favorably with that of chloroquine.

Amodiaquine has produced favorable results, similar to those obtained with chloroquine, in discoid lupus erythematosus. Doses of 800 mg. /day have been employed.

**Toxicity.** The acute and chronic toxicity of amodiaquine in laboratory animals is quite low. In the treatment of malaria the drug has produced nausea, vomiting, salivation, and diarrhea. Central nervous system effects of lack of coordination, spasticity, and convulsions have been reported. Untoward side effects are seldom encountered, however, in the usual recommended doses in malaria therapy. The presence of liver or kidney disease is not a contraindication to the use of amodiaquine in malaria.

In the doses employed in discoid lupus erythematosus or rheumatoid arthritis, amodiaquine has produced pancytopenia, jaundice, hepatitis, fever, and fatal agranulocytosis (Perry *et al.*, 1962).

**Chlorguanide Hydrochloride (Paludrine)** is the salt of the base N-1-(*p*-chlorophenyl)-N-5-isopropyl biguanide.

The early experiences with chlorguanide were not fully substantiated in succeeding years. The drug is an effective suppressive against *P. vivax*, but all parasites are not eradicated, and infections appear after the drug is discontinued. Chloroquine is superior to chlorguanide in the treatment of vivax malaria.

When chlorguanide is taken orally, about half the dose is excreted in the urine, and the major metabolite is 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine, called chlorguanide triazine (Carrington *et al.*, 1951). The very rapid excretion of this triazine metabolite in the urine following its oral administration prevented the use of the metabolite as an important antimalarial drug.

In their search for an antimalarial with a prolonged action, Thompson *et al.* (1963) synthesized the pamoate derivative of the dihydrotriazine metabolite of chlorguanide. This compound is 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-trizine pamoate. It is called chlorguanide triazine pamoate, or CI-501.

**Chlorguanide triazine pamoate.** Mice were protected for weeks and monkeys for many months by this repository antimalarial, when challenged with blood stages of *P. berghei* and *P. cynomolgi*. Its low aqueous solubility (0.003 per cent) permitted the drug to dissolve very slowly and without tissue encapsulation. Slow release of the dihydrotriazine component and its rapid excretion preclude the attainment of a high plasma level. The rapid excretion of the drug after its release from the injection site minimizes the likelihood of systemic toxicity. The potency of the drug to inhibit the growth of parasites in the blood is demonstrated by the extremely low protective plasma levels of less than 0.006 μg/ml. The first report on this new drug comments on the exceedingly small amount of an antimalarial drug that can prevent the growth of malarial parasites.

A single dose equivalent to 50 mg/kg. of the base of chlorguanide triazine pamoate suspended in castor oil, injected intramuscularly in monkeys, conferred protection against repeated sporozoite challenges for at least 6 months, and in some individuals for as long as 11 to 15 months. The drug provided protection against massive doses of sporozoites and proved to be effective in clearing established infections (Schmidt *et al.*, 1963).

In human volunteers at the United States Penitentiary at Atlanta, Georgia, the repository preparation of chlorguanide triazine pamoate was demonstrated to have the capacity to give long-term protection against human vivax malaria (Coatney *et al.*, 1963). A single intramuscular injection of a dose of 5 mg. of the base per kg. protected against the Chesson strain of *P. vivax* either by bites of heavily infected mosquitos or by intravenous inoculations of parasitized homologous blood. Some subjects were exposed to infection in this way 10 times. The duration of protection ranged from 9 to 12 months for 20 of the 24 volunteers. The shortest protection time was slightly over 5 months for 1 subject. Four infected control volunteers were treated therapeutically with the repository preparation, and the response was equal to that of chloroquine.

It is too early to assess the true significance of these observations. Public health specialists all testify to the difficulty of getting large numbers of people to continue taking preventive medication over long periods of time. If a single injection once or twice a year can accomplish this goal, a major advance in the fight against malaria will have been made.

### 8-Aminoquinoline Derivatives

**Pamaquine naphthoate (Plasmochin).** This drug is a yellow, odorless, tasteless powder. It is insoluble in water. Pamaquine is 6-methoxy-8-(4-diethylamino-6-methylbutylamino)-quinoline.

Pamaquine possesses a relatively weak action against the asexual erythrocytic forms, and other drugs are superior in this regard. It will destroy the persistent forms responsible for vivax malaria relapses. This activity is enhanced by the simultaneous administration of quinine.

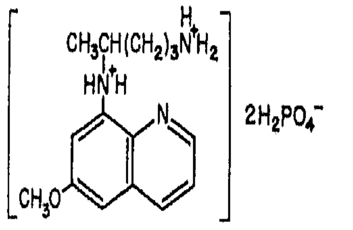
**Toxicity.** Experiences with pamaquine during World War II indicated that this drug was not as safe to employ on a large scale as quinacrine. Pamaquine produces methemoglobinemia, cyanosis, and may produce hemolytic jaundice. Individuals under therapy have experienced abdominal pain, gastrointestinal disturbances, weakness, and collapse. The drug occasionally produces acute intravascular hemolysis. This serious reaction is more common in Negroes.

The toxicity of pamaquine places serious limits on its usefulness. However, its curative activity indicated that more effective or less toxic 8-aminoquinoline compounds might be found. Pentaquine and primaquine resulted from studies to find such drugs.

**Pentaquine.** Pentaquine is 6-methoxy-8-(5-isopropylaminoamylamino)-quinoline. Pentaquine, closely related chemically to pamaquine, was found to be effective in the treatment of *relapsing* vivax malaria. Unfortunately, pentaquine proved to be too toxic for extensive use in malaria. The incidence of methemoglobinemia and acute hemolytic anemia in heavily pigmented races was quite high. Its effectiveness, however, stimulated the search for less toxic 8-aminoquinolines. Primaquine was discovered in these studies.

**Primaquine Phosphate, U.S.P.** Primaquine was first synthesized as an outgrowth of the World War II antimalarial program. It is a less toxic 8-aminoquinoline with potent antimalarial activity. Primaquine is 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline diphosphate.

Primaquine is supplied as tablets containing 26.3 mg. of primaquine diphosphate equivalent to 15 mg. of primaquine base. The dose is customarily expressed in terms of the base. A daily dosage schedule of one tablet (15 mg. of the base) is usually given for 14 days. This drug is used for the radical cure and prevention of relapses of vivax malaria. In the treatment of the symptoms of a primary attack or a relapse of vivax malaria, the same dose of primaquine is given with a 3-day course of chloroquine or amodiaquine. The special problem of primaquine toxicity is discussed in the following section.



Primaquine Phosphate, U.S.P.

Primaquine is active against primary exoerythrocytic forms of *P. vivax* and against *P. falciparum*. This drug is gametocidal to all forms of malaria parasites; it is not active against the asexual blood forms of *P. falciparum*. It is very effective in curing subclinical malaria and preventing relapses. It is the drug of choice for this purpose in vivax malaria, since it destroys the tissue forms which give rise to secondary erythrocytic parasites that cause the relapse. Primaquine has greater effectiveness and less toxicity in clearing the late tissue forms of *P. vivax* than any other drug. It is used only for the prevention of relapses of vivax malaria and for radical cure of the disease.

The standard method employed for chemoprophylaxis of malaria is as follows: while the patient is in a malarious area, 300 mg. of chloroquine base is administered once a week. Upon leaving the malarious area, the patient receives 600 mg. of chloroquine base plus 15 mg. of primaquine base on the first day of departure, followed by 15 mg. of primaquine for the next 13 days.

In controlled clinical trials, Alving *et al.* (1960) reported that the weekly administration of 300 mg. of chloroquine base and 45 mg. of primaquine base was highly effective as a prophylactic against severe *P. vivax* infections. A mass trial of this dosage regimen in over 50,000 adults, personnel of the U. S. Eighth Army in Korea, indicated that the dosage was safe. No greater toxic reactions were encountered than those previously observed with chloroquine alone (Vivona *et al.*, 1961).

### Hemolytic Effect of Antimalarial Drugs

The hazards of hemolytic reactions, which follow the administration of a number of drugs, were emphasized by the discovery of a biochemical genetic basis for these effects. The findings of Hockwald *et al.* (1952) that the hemolytic effect of primaquine was individualistic and the subsequent demonstration by Dern (1954) that this abnormality was related to the person's erythrocytes, led Beutler *et al.* (1955) and others to the conclusion that this intrinsic defect is characterized by several biochemical abnormalities. Work in this important area of drug toxicity has been highlighted by studies on primaquine-sensitive individuals, and therefore the subject is discussed in detail in this chapter. About 16 pharmacologically different drugs have been shown to produce hemolytic effects in therapeutic doses in individuals with biochemical genetic patterns that can be identified. Primaquine sensitivity is reviewed in detail as illustrative; other examples are referred to in the following section and in the text under the discussion of the pharmacology of the specific drug. The subject has been reviewed by Kellermeyer *et al.* (1962).

### Primaquine sensitivity.

Like the other 8-aminoquinolines, primaquine may produce severe hemolytic anemia, methemoglobinemia, and leukopenia, especially after large doses or in susceptible subjects. The incidence of these untoward reactions appears to be low.

Hockwald and co-workers (1952) demonstrated that approximately 10 per cent of American Negroes and a very small number of Caucasians will develop hemolytic anemia when given an average dose of primaquine. The severity of primaquine-induced hemolysis depended on the dosage and occurred in the same individuals who were susceptible to hemolysis by pamaquine. Beutler (1955 *et seq.*) and others have noted that the hemolytic effect of primaquine is the result of an intrinsic abnormality of the red blood cells. The red cells of susceptible individuals possess a reduced concentration of glutathione, and there is a deficiency of glucose-6-phosphate dehydrogenase activity. According to Kellermeyer *et al.* (1962), individuals whose erythrocytes are deficient in glucose-6-phosphate dehydrogenase and who will experience clinical hemolysis following the ingestion of 30 mg. of primaquine daily are referred to as "primaquine-sensitive." This reaction does not imply an allergic or immune process.

The abnormality is apparently related to a sex-linked gene of intermediate dominance. The erythrocytes of these persons have no known deleterious effect on the individual and have a normal life span. It should be pointed out that *excessive* doses of primaquine and related 8-aminoquinolines will likely produce hemolytic anemia in all individuals. In sensitive subjects with this gene-linked erythrocyte abnormality, even *small* doses may precipitate the hemolytic effect.

The diagnosis of primaquine sensitivity is established by laboratory tests. Five such tests have been devised: assays of glucose-6-phosphate dehydrogenase of erythrocytes (Kornberg and Horecker, 1955); a glutathione stability test that measures the disappearance of glutathione from erythrocytes during aerobic incubation with glucose and acetylphenylhydrazine (Beutler *et al.*, 1955); Heinz body formation in erythrocytes incubated with acetylphenylhydrazine (Beutler *et al.*, 1955); a brilliant cresyl blue dye test that presumably measures reduced triphosphopyridine nucleotide generated by erythrocytes (Motulsky, 1960); and the methemoglobin reduction test of Brewer *et al.* (1962). The latter test is practical, accurate, and easily performed. It is based on the inability of sensitive cells to reduce methemoglobin in the presence of methylene blue under aerobic conditions. This test identifies individuals who will experience hemolysis of clinical significance during the administration of many drugs. Patients inherently vulnerable to drug-induced hemolytic episodes may be identified.

Although the severity of the drug-induced hemolysis in primaquine-sensitive individuals is often mild, many extracorpuscular factors can enhance the hemolytic susceptibility. Systemic diseases and pathologic states most often potentiate the hemolysis and produce severe episodes.

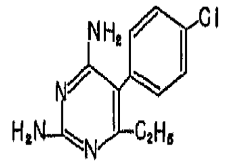
The distribution and genetic transmission of the primaquine-sensitive trait and its associated glucose-6-phosphate dehydrogenase deficiency has been studied intensively. In addition to its pharmacogenetic significance, the enzyme deficiency is of interest because it is apparently associated with at least 4 x-chromosome linked mutations in man (McKusick, 1962). The trait is ubiquitous, and the incidence varies greatly in different racial and ethnic groups. The highest incidence occurs among Kurdish Jews (60 per cent), the lowest among Caucasians of non-Mediterranean origin (less than 1 per cent). In U. S. Negroes the incidence is about 10 per cent; a relatively high incidence is found in dark-skinned Jews of Asiatic and Mediterranean origin, Sardinians, some African Negro tribes, Iranians, Asiatic Indians, and Filipinos. The enzyme deficiency is not found in North American Indians or Alaskan Eskimos. Kellermeyer *et al.* (1962) estimate that the enzyme defect probably affects more than 100 million of the world's people. The interesting point is made by these authors that the defect may provide a biologic advantage in areas where *P. falciparum* is endemic. It may mitigate the severity of the malarial infection in infants and young children.

It is likely that the deficiency in glucose-6-phosphate dehydrogenase is not limited to erythrocytes. It has been demonstrated in other cells of the body of sensitive persons—platelets, leukocytes, liver, and skin. These findings suggest that the concept of biochemical individuality based upon genetic background has a correlation with the pharmacodynamics of a drug.

Many drugs, foods, and chemicals have been implicated in causing acute intravascular hemolysis in susceptible individuals. The erythrocytes of these persons have a diminished activity of the enzyme glucose-6-phosphate dehydrogenase, and, usually, of the reduced form of glutathione and of catalase. The nitrofurans, sulfonamides, acetophenetidin, acetylsalicylic acid, menadione sodium bisulfite, fava beans, primaquine and related 8-aminoquinolines, chloramphenicol, acetanilid, and naphthalene have been identified as capable of eliciting these untoward effects even in moderate doses in susceptible individuals.

### Diaminopyrimidine Derivative

**Pyrimethamine, U.S.P. (Daraprim)** is a tasteless, odorless, white crystalline powder, non-hygroscopic and stable at room temperature. Pyrimethamine base is only slightly soluble in water. It forms soluble acetate and lactate salts. Pyrimethamine base is 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine.



Pyrimethamine, U.S.P.

Pyrimethamine was discovered by Hitchings and co-workers in a series of investigations extending over a period of years on antagonists to nucleic acid derivatives. The theoretical aspects of this study were described in the section on the chemistry of the antimalarial drugs. Pyrimethamine emerged as the most active of about 300 compounds of a series of diaminopyrimidines synthesized and investigated pharmacologically.

A number of clinical investigations have shown pyrimethamine to be an effective suppressant antimalarial drug. It is active in very small oral doses at weekly intervals. Because it is tasteless and odorless and well tolerated by children and adults, it promises to be most suitable for mass control of malaria in endemic regions. There are numerous records that suggest that pyrimethamine may slowly sterilize the tissue forms of *P. vivax* and thus produce a radical cure. At present, however, it is employed as a suppressive drug only. It appears that in patients under therapy the mosquito-transmissible sexual forms of the parasite are so modified that they fail to develop infective sporozoites. Thus pyrimethamine therapy could become a useful factor in transmission control of the infection.

**Administration.** For suppressive prophylaxis one 25-mg. tablet of pyrimethamine weekly is considered adequate for adults. The dose for children under 15 years is one-half tablet weekly.

Pyrimethamine should not be used alone in the treatment of acute attacks of malaria. The faster-acting schizonticides chloroquine or quinacrine are preferable. Pyrimethamine is a slower-acting drug, depending in part upon the age of the trophozoites in the host when the drug is administered. The simultaneous administration of pyrimethamine and a fast-acting schizonticide, in doses of 25 mg. daily for 2 days, is said to initiate transmission control by arresting sporogony in the mosquito.

The chief advantage of pyrimethamine seems to lie in the fact that once clinical cure of an acute attack of malaria has been obtained, a regimen of 25 mg. once weekly will provide long-term suppression.

**Development of resistance.** It has been possible to develop resistant laboratory strains of malaria when pyrimethamine was administered in subcurative dosages. Hernandez *et al.* (1953) were able to achieve a 25-fold resistance to pyrimethamine in male volunteers by treating blood-inoculated infections of *P. vivax* with gradually increasing doses of the drug. These pyrimethamine-resistant infections were sensitive to chloroquine. They point out, however, that it is unlikely that resistance to pyrimethamine will become a serious problem under therapy; it required very careful planning to develop this resistance under experimental conditions.

Primary resistance to pyrimethamine does not develop when it is used as a suppressant in small weekly doses. Cross-resistance to chlorguanide exists. For this reason the drug should not be used if chlorguanide has previously been employed.

**Toxicity.** Pyrimethamine in therapeutic doses has not produced toxic manifestations in extensive field trials. Because pyrimethamine is a potent and long-acting drug, administration for suppressive prophylaxis should be limited to malarial seasons, and the dose should not exceed the recommended weekly amount. To guard against the possibility of interference with hematopoiesis, the drug should be discontinued pending an investigation in the event of an unexplained fall in erythrocyte count.

Pyrimethamine is generally considered to have a wide margin of safety in the therapeutic doses employed. Because the drug is a folic acid antagonist, it may produce the symptoms of folic acid deficiency, *i.e.*, megaloblastic anemia or leukopenia. Cases of fatal poisoning have been reported following overdosage of pyrimethamine.

### The Pharmacology of Quinine

**Quinine, N.F.** The cinchona tree is indigenous to the forests of South America. The bark of the tree found growing in the wild state is quite low in alkaloidal content. As a result of the Dutch cultivation of cinchona in Java and the British government plantations and hybridization studies in India, the yield of alkaloid obtained from the bark was increased to as much as 18 per cent.

Fourteen natural *d* and *l* alkaloids have been characterized from the root and stem bark of *Cinchona succirubra*. Therapeutically, the most important are quinine and quinidine. In 1820, Pelletier and Caventou first isolated the bases cinchonine and quinine and demonstrated that the antipyretic properties of the bark depended upon the alkaloid content. Pasteur in 1852 established the isomeric relationship of the alkaloids quinine, quinidine, cinchonine, and cinchonidine, and Justus von Liebig determined the empirical formula of quinine in 1838.

**Local action.** Quinine is a protoplasmic poison. It interferes with the nutrition, reproduction, and motility of nearly all cells. *In vitro*, quinine is toxic to trypanosomes, infusoria, plasmodia, and spermatozoa. Its action in malaria depends upon a more specific effect upon the plasmodium than on the elements of blood.

In contact with sensory nerves quinine produces a brief stimulation and then paralysis. This action is directly proportional to its toxicity to protoplasm. Solutions of quinine injected subcutaneously are painful; they produce local irritation and anesthesia. Abscess formation may result. Quinine and Urea Hydrochloride Injection, N.F., is used as a sclerosing agent for injection in the obliterative treatment of varicose veins.

**Fate in the body.** After the administration of usual therapeutic doses of quinine, the compound appears in the urine within a few minutes. Approximately 20 per cent is eliminated in the urine unchanged or conjugated with glycuronic acid. Quinine may be detected in the urine 72 hours after administration. Only traces are found in other excretions; the remainder undergoes destruction in the tissues.

Quinine penetrates the red blood cells and produces hemolysis in concentrations of 1 in 700. Quinine is said to render the red blood cells more susceptible to the action of tissue lytic factors and saponin.

**Action on the heart.** The heart function is depressed by quinine. This is the result of direct action on heart muscle and vagus stimulation. The cardiac depression may result in a fall in blood pressure. Peripheral vascular dilation as a result of quinine action may accentuate the fall in blood pressure. In therapeutic oral doses the cardiac effects are not observed and do not constitute a clinical problem. Quinidine, the *d*-isomer of quinine, on the other hand, has a more specific action on the myocardium. It is a reliable therapeutic agent in the treatment of atrial fibrillation (see page 656).

**Action on skeletal muscle.** Quinine produces a depression of the activity of skeletal muscle. It aggravates myasthenia gravis (see page 589). The alkaloid is used in the treatment of *congenital myotonia* because of its curarizing action on skeletal muscle.

**Action on body temperature.** In malarial fever, quinine has a direct action on the organism causing the disease and thus suppresses the elevated body temperature. In other febrile conditions quinine may exercise a true *antipyretic* effect. In these conditions it is similar to other antipyretic and analgesic drugs. Like the salicylates, this action is on the temperature-regulating centers, increasing body heat loss. The effect of quinine on normal body temperature is negligible.

**Toxicology.** Except in idiosyncratic individuals, ordinary doses have no effect on the eye. After massive doses or in persons sensitive to quinine, profound changes in visual acuity (*quinine amblyopia*) or even blindness may result. An edema and anemia of the retina with constriction of the retinal arteries may occur. The vascular effect resulting from prolonged treatment with quinine has produced optic atrophy. *Photophobia, blurred vision,* and *diplopia* are frequent findings in patients taking quinine for long periods of time.

Large therapeutic doses of quinine in the normal individual and as little as 0.3 gm. in the hypersensitive person frequently produce a ringing in the ears. The *tinnitus aurium* is related to the blood quinine concentration. When the drug leaves the circulation, the symptom disappears. When quinine was used in treating malaria, this symptom of medication was frequently distressing. Prolonged treatment has been known to produce deafness. The auditory symptoms have been ascribed to a congestion and hemorrhage in the tympanum and labyrinth. Degenerative changes have been described in the spiral ganglion in the cochlea. The use of quinine preparations for the treatment of upper respiratory tract infections of aircraft pilots may seriously interfere with their hearing (Waters, 1960).

In therapy with quinine and related alkaloids, the larger therapeutic doses produce a group of symptoms referred to as *cinchonism.* These symptoms of the eye and ear, previously described, may be associated with mental confusion, severe headache, skin eruptions, and edema of mucous membranes. Nausea and gastrointestinal symptoms are frequently observed resulting from local and central effects. The degree of sensitivity of the individual determines the extent of the reactions to the drug. In hypersensitive individuals a single dose may elicit toxic manifestations.

Very large doses of quinine produce major toxic reactions. There are auditory and visual disturbances, confusion, delirium, fever, and apprehension, followed by loss of consciousness. Respiration is first stimulated, then depressed and shallow. Cyanosis may develop, the body temperature falls, and the pulse becomes feeble. Death occurs from respiratory paralysis. Acutely toxic doses may produce death within a few hours. The degree of absorption from the gastrointestinal tract determines the extent of the poisoning. Quinine sulfate is relatively less soluble than the other salts, and recovery from massive doses (8 to 30 gm.) has been reported. After toxic doses of quinine, albuminuria may be present; hemoglobinuria is a less common finding. Individuals recovering from severe intoxication may exhibit a disturbed visual and auditory pattern.

**General therapeutic uses.** Quinine has been a popular drug in the relief of myalgia, neuralgia, headache, and as an antipyretic. It is less effective than the salicylates and may produce alarming reactions in the idiosyncratic person. The usual dose is between 0.06 and 0.3 gm. Its use in the treatment of the common cold appears to be empirical and symptomatic. There seems to be little justification for use of a potentially toxic drug in conditions of this character.

The salts of the alkaloid quinine are generally employed. Of these the sulfate and the hydrochloride in the form of tablets or capsules are most commonly used. Palatable preparations of quinine sulfate in a *cocoa syrup* are available for children unable to swallow a tablet or capsule.

**Administration in malaria.** Quinine sulfate in the form of 0.6-gm. tablets 3 times daily after meals for 3 to 4 days, or until fever is controlled, has been found most effective. Quinine in this dosage is a suppressive drug. The low potency of quinine as a suppressive drug and its toxicity make its place secondary to the synthetic antimalarials in therapy. It is of interest that quinine alone was found to be effective in curing the recently discovered cases of falciparum malaria from Southeast Asia that were resistant to all other antimalarial agents. However, very large doses of 4 gm./day were required.

### Chemotherapy of Other Infectious Diseases

A general outline of these infectious diseases is as follows:

1. Viruses
   a. Yellow fever
   b. Smallpox
   c. Lymphogranuloma venereum
2. Rickettsia
   a. Typhus and rickettsial infections
3. Bacteria
   a. Cholera, *Vibrio comma*
   b. Bacillary dysentery, *Shigella dysenteriae*
   c. Plague, *Pasteurella pestis*
   d. Leprosy, *Mycobacterium leprae*
4. Spirochetes
   a. Relapsing fever, *Borrelia recurrentis*
   b. Yaws, *Treponema pertenue*
   c. Weil's disease, *Leptospira icterohaemorrhagiae*
5. Fungi
   a. Dermal mycoses
   b. Candidiasis, *Candida albicans*
   c. Torulosis, cryptococcosis, *Cryptococcus neoformans*
6. Protozoa
   a. Amebic dysentery, *Entamoeba histolytica*
   b. Trypanosomiasis, *Trypanosoma gambiense*
   c. Chagas' disease, *Trypanosoma cruzi*
   d. Leishmaniasis, *Leishmania donovani*, related species
   e. Malaria
7. Helminths
8. Trematodes
   a. Schistosomiasis, *Schistosoma* species
9. Nematodes
   a. Filariasis, *Wuchereria bancrofti*, related species
   b. Dracunculus, *Dracunculus medinensis*
10. Arthropods
   a. Scabies, *Sarcoptes scabiei*

The therapy of these infectious diseases is beyond the scope of this text. However, to give a better understanding of the role of pharmacotherapy, a brief outline is presented. Only certain of these infectious diseases are considered, especially those that have responded most satisfactorily to chemotherapy.

### Lymphogranuloma venereum.

Lymphogranuloma venereum is a chronic infection of an ulcerative nature. It is a widespread, communicable disease, usually acquired venereally. The disease is caused by a specific filterable virus that differs to some extent from the typical filterable viruses. The specific agent can produce infection in experimental animals. In man, the infective agent usually gains access to the body through the skin or mucous membranes of the external genitalia.

The disease is now thought to be much more common than had been generally recognized. It is present in many parts of the world, including tropical and nontropical areas. It is found in all races and shows a high incidence among Negroes in the United States. A survey of clinics and hospitals in the United States has indicated that the disease is to be found in both whites and Negroes of all social levels and in individuals who have never been in tropical regions.

Lymphogranuloma venereum occurs more frequently within the age limits of greater sexual activity. According to surveys of this disease, there is a comparatively high incidence among the sexually promiscuous. The disease begins with a small erosion following infectious contact and, in the male, within 1 to 2 weeks may involve the inguinal lymph nodes with multiple suppuration and fistula formation. In the female, by retrograde involvement of the pelvic lymphatics, it tends to ulceration and *elephantiasis* of the vulva and perineal region with rectal stricture. The primary lesion is painless. Eventual constitutional symptoms of *fever, anorexia,* and *rheumatoid* pains with *erythema multiforme* may develop. The involvement of the lymphatic nodes with swelling and suppuration leads to the formation of multiple chronic fistulas. Lymphogranuloma venereum has been treated by the use of the antimonial, stibophen. The sulfonamide drugs are of value in the early acute stages of the disease; however, the most satisfactory therapy has been achieved by the use of the broad-spectrum antibiotics.

### Granuloma inguinale (granuloma venereum).

This is a mildly contagious, chronic, progressive disease involving the skin and occasionally the lymphatics, usually in the inguinal region. The etiologic agent is *Donovania granulomatis*, a pleomorphic, rod-shaped organism occurring intracellularly. It is generally regarded as a venereal disease. The first evidence of infection is the appearance of a vesicle, or nodule, usually on the genitalia. The early lesions may appear as small elevations or as a fine granular film covering the glans. Nodules beneath the skin may be present. These lesions are not painful. The inguinal manifestations appear secondarily to the genital lesions. These are slow to heal and gradually spread to adjacent skin areas. Ulcerative lesions that remain stationary for many years may result. The disease is frequently complicated by other venereally acquired infections. Granuloma inguinale may be diagnosed by the characteristic Donovan bodies which appear in smears from granulation tissue. Antibiotic therapy has proved to be very successful in the treatment of this disease, although the antimonials are also effective.

### Schistosomiasis (bilharziasis).

This disease is caused by a blood fluke. Three species have been described, *Schistosoma hematobium*, *S. mansoni*, and *S. japonicum*. The cercariae of the flukes pierce the skin or mucous membranes of individuals bathing in contaminated water. They enter the venous system and mature in the liver. When they become mature, they migrate to the intestinal venules, where the female deposits enormous numbers of eggs. The flukes produce local inflammatory reactions, particularly in the bladder. *Cystitis* and *ulceration* may result in *hematuria* and *dysuria*. The disease is frequently complicated with *urinary calculi*.

Schistosomiasis has an endemic distribution in Africa, Syria, West Indies, northern South America, Japan, Formosa, China, Philippines, the Celebes, and Egypt.

The effective agents in schistosomiasis are tartar emetic, stibophen, and lucanthone.

### Leishmaniasis (kala-azar).

This is a tropical disease caused by the protozoan organism *Leishmania*. In various regions of the world different strains of the *Leishmania* have been recognized. There are three forms of the disease, visceral, dermal, and mucocutaneous, usually regarded as being caused by three separate species, *L. donovani*, *L. tropica*, and *L. brasiliensis*. The disease is transmitted by the sand fly *Phlebotomus papatsi* and related species. It is highly endemic in the Mediterranean area, India, and China. The organisms imbed themselves in the endothelial cells lining the blood and lymph vessels, where they are eventually released into the blood and lymph streams. *Fever*, *emaciation*, and *anemia* with a *leukopenia* are symptoms of the visceral form of the disease. The body of an individual suffering from this disease may assume a dusky hue (kala-azar means "black sickness"). Tremendous distention of the abdomen may result from splenic and hepatic enlargement. The disease has a high mortality rate.

The organic antimony compounds and hydroxystilbamidine are most effective in the treatment of leishmaniasis.

### Trypanosomiasis (African sleeping sickness).

The disease is caused by the *Trypanosoma gambiense* and *T. rhodesiense*. The organism gains access to the body by the bite of the tsetse fly, *Glossina palpalis* and *Glossina morsitans*, which serves as an intermediate host for the parasite. The animal host is the *antelope*, the tsetse fly being the vector. The degree of mortality of this disease is high. The symptoms are *lassitude*, *weakness*, *prolonged lethargy*, and *coma*. Antimony compounds are useful in the treatment of this disease, and suramin is effective in the early stages of the infection. Suramin has proved to be especially useful in *T. rhodesiense* infections. Pentamidine is most useful in *T. gambiense* infections, particularly in early infections or when used prophylactically.

South American trypanosomiasis (*Chagas' disease*) is caused by *T. cruzi* and is found in South and Central America and Mexico. This disease is transmitted usually through the feces of *reduviid bugs* of the family *Triatomidae*. The treatment of this disease with chemotherapeutic agents has been quite unsatisfactory.

### Filariasis.

Two species of filarid worms, *Wuchereria bancrofti* and *W. malayi*, cause the disease filariasis. The disease is widely distributed in tropical and subtropical countries. Filariasis was introduced into the southeastern portion of the United States with the advent of slavery. The disease gradually decreased in incidence until about 1925. Since then, little or no evidence of filariasis has been reported. During World War II several thousand servicemen contracted the infection in the Pacific islands.

Certain species of Culex mosquito serve as the vector for the disease. The transmission of the disease thus resembles malaria. When the mosquito bites an individual, the larvae escape and enter the puncture wound. From here they find their way into the peripheral lymphatics. The pathologic changes are caused by the production of living embryos in the blood and tissues. The disease is characterized by *specific lesions in the lymphatic glands*, *fibrosis*, *focal necrosis*, and *giant-cell inflammation*. Microfilariae are retained in the glands, die, and become cretified. Elephantiasis of the arms and legs, breast, or scrotum is a typical pathologic symptom. The disease has a high degree of chronicity, with fever, chills, fatigue, and muscle pain.

No chemotherapeutic agent is known that will prevent an individual from becoming infected. The vector mosquito is readily controlled and the greatest success in curbing this disease has been by mosquito control methods. The disease in man has been treated successfully with diethylcarbamazine.

### Yaws (frambesia).

Yaws is a chronic contagious disease found in tropical countries. The disease resembles syphilis but is nonvenereal. It is characterized by primary and secondary sores and caused by a spirochete, the *Treponema pertenue*. The organism is morphologically indistinguishable from *T. pallidum* of syphilis. The clinical features of yaws follow an incubation period of from 3 to 4 weeks. A primary sore at the site of inoculation, which is usually not on the genitalia, is frequently the first symptom. *Malaise*, *rheumatic pains*, and *pyrexia* are symptoms of this stage of the disease. The secondary stage occurs within 3 months after the primary lesion. This stage is characterized by eruptions of the skin with dry, minute papules and evidence of systemic infection, such as headache and fever. The typical skin lesions are raspberry-like excrescences or "yaws." These are not painful but itch intensely. A tertiary stage of the disease, which follows within 6 months to 2 years, is associated with gummatous nodules and indolent ulcerations resulting in scar contractures and painful deformities. The disease is benign and the mortality rate is low. Arsenical and antimonial therapy has been successful in this disease, but in recent years the antibiotics provide the most satisfactory form of treatment.

### Leprosy.

Leprosy, also known as Hansen's disease, is a chronic, mildly contagious, infectious disease characterized by local cutaneous lesions and systemic symptoms. Various deformities may occur. The disease in many respects resembles tuberculosis. The causative organism is believed to be the *Mycobacterium leprae*, although the mode of transmission is not known. For many years the only drug available to treat leprosy was chaulmoogra oil. At present sulfone therapy is the treatment of choice, although streptomycin is also effective.

The onset of the disease is insidious, with a gradual development of lesions of the skin. These are light red, purple, or bronze macules and infiltrated yellow nodules. There may be areas of alopecia. Symptoms of anesthesia of an extremity with a painful neuritis and various paresthesias are neurologic manifestations. Contractures of the fingers or toes with bone absorption and trophic ulcers are characteristic. Numerous systemic manifestations, *e.g.*, anemia, enlargement of the lymph nodes, acute febrile episodes, and an associated erythema, are exhibited by leprosy patients. Lesions of the eye and nasopharynx are common. With institutional care and drug therapy, the prognosis is good. After a prolonged period of therapy, acid-fast bacilli can no longer be demonstrated in the scar tissue, and the disease may be considered to be arrested.

## The Organometallic Compounds in the Chemotherapy of Infectious Diseases

Organic compounds of arsenic and bismuth are used to a limited extent in modern therapeutics. Because these drugs are no longer the prominent medicinal agents they formerly were, only brief mention will be made of their pharmacology in this edition of the text. The use of antibiotics in the treatment of syphilis and a number of the tropical diseases is considered in Chapter 10.

### The organic arsenicals.

**History.** In the fifth group of the periodic chart of the atoms associated with nitrogen and phosphorus, one finds three elements of chemotherapeutic significance, namely, arsenic, antimony and bismuth. One of the first chemotherapeutic organic compounds of arsenic to be prepared was the sodium salt of aminophenylarsenate, an aromatic arsenical called *atoxyl*.

The discoveries with atoxyl attracted the attention of Paul Ehrlich, who had been working with trypan red and the basic triphenylamine dyes in mouse trypanosomiasis. Apparently Ehrlich conceived of the idea of modifying atoxyl to render it a more active and less toxic compound. Fortunately he was associated with an excellent chemist, Bertheim, who with Ehrlich in 1907 demonstrated that atoxyl was 4-aminobenzenearsonic acid. This discovery suggested numerous syntheses, and their attention was turned to the preparation of modifications of this molecule. Among the compounds Ehrlich and Bertheim prepared were two that were destined to play dramatic roles in the chemotherapy of infectious disease. These were oxophenarsine and arsphenamine.

Ehrlich concluded that arsphenamine was superior to any of the compounds that he had studied, and in 1910 this drug was introduced into therapeutics for the treatment of syphilis under the trade name of *Salvarsan*. Ehrlich and Hata reported it as the 606th compound of their series, and the drug became known popularly as "606."

In 1934 Tatum and Cooper reexamined the pharmacodynamics of the arsphenamines and concluded that *Mapharsen*, Ehrlich's oxophenarsine, was superior to arsphenamine in experimental syphilis.

In his numerous papers Ehrlich considered the arsphenamines to be directly toxic to trypanosomes and spirochetes. This view is not held at the present time. Ehrlich's conception of a "toxophoric" group attaching itself to the parasite and hence destroying the organism while not attacking the tissue cells of the host is no longer considered a satisfactory explanation of the mechanism of action of the organic arsenicals. His hypothesis served a valuable purpose however, in stimulating the new science of chemotherapy to the further synthesis of compounds possessing low toxicity and intense parasiticidal action. His conception of a drug with a high therapeutic index served as a model for chemotherapeutic studies for many years.

Mellon (1938) has pointed out the disadvantages of the concept of the *chemotherapeutic index* as suggested by Ehrlich, that is to say, the evaluation of a drug based upon its capacity to destroy all the spirochetes in the body in one dose without appreciable injury to the tissues of the host. A drug having such properties would be considered *parasitotropic*. Such a concept ignores the possibility of the host's ability to mobilize its own cellular defenses. The discovery of the sulfonamides and antibiotics focused attention upon this latter mechanism of anti-bacterial action. This approach to the control of infection appears to be more fruitful.

**Oxophenarsine Hydrochloride, N.F. (Mapharsen).** This is a trivalent organic arsenical employed medicinally as a mixture with buffering agents and suitable substances to render its solutions physiologically compatible with human blood. It is a white or nearly white odorless powder, soluble in water. It is 3-amino-4-hydroxyphenyl arsinoxide hydrochloride.

A solution is prepared by adding the contents of a single dose ampule to 10 ml. of sterile distilled water in a sterile glass container and stirring vigorously until the drug is completely dissolved. The solution may be freely aerated. It is injected rapidly intravenously. Failure to inject solutions of oxophenarsine rapidly may cause pain along the course of the injected vein.

*Therapeutic use.* Oxophenarsine is employed only in those rare cases of syphilis that do not respond to antibiotic therapy. Syphilotherapy is a difficult medical problem when an organic arsenical drug is employed. For these reasons, the details of medication are omitted and the student should consult the references cited.

Vincent's angina (tonsillopharyngitis) has been treated by intravenous oxophenarsine hydrochloride and the topical application of a 5 per cent solution to the mucous membranes of the mouth and throat. Penicillin administered systemically, however, is the preferred treatment. Arsenical therapy has also been used in such conditions as lupus erythematosus and pemphigus, although the rationale of such use is questionable.

CARL VOEGTLIN
1879–1960
*Eminent investigator in the field of chemotherapy*
"In all events, the extension of our theoretical knowledge is bound to lead, as it has led in the past, to important practical applications in the cure and prevention of certain diseases by these chemotherapeutic agents."

**Tryparsamide, U.S.P.,** is a pentavalent organic arsenical. It is the monosodium salt of *p*-N-phenylglycineamidoarsonic acid. It is a white, odorless, crystalline powder, soluble in water.

This compound of arsenic was introduced into therapeutics as a trypanocidal agent in the treatment of *T. gambiense* trypanosomiasis. It has also been employed in the treatment of resistant cases of syphilis of the central nervous system. The most serious complication following tryparsamide therapy is visual damage. The symptoms consist of a contraction of the visual fields and blurred vision. Pentavalent arsenic compounds of the tryparsamide type must be reduced in the body to trivalent arsenic form before they are spirocheticidal.

The usual dose of tryparsamide as an antitrypanosomal drug is 1 to 3 gm. intravenously, depending upon the body weight and the physical condition of the patient.

**Arsthinol (Balarsen).** This drug is a trivalent arsenical employed in the treatment of intestinal amebiasis and yaws. It is discussed in Chapter 13.

**Toxic reactions to the organic arsenicals.** The incidence of untoward reactions of these agents is very high. Acute arsenical reactions of a systemic character resembling a shock-like state may be encountered. *Angioneurotic reactions*, *dermatitis*, *nausea*, *vomiting*, *diarrhea*, and possibly *liver damage* may follow their intravenous administration. Very close medical supervision should be exercised if these drugs are used.

All tissues of the body may retain some arsenic after therapy with the organic arsenicals. The bones, skin, hair, and fingernails, for example, have been shown to contain abnormally high amounts for long periods of time. The glutathione content of the particular tissue seems to determine the extent of arsenic retained.

*Acute arsenic poisoning.* Acute arsenic poisoning resulting from the ingestion of arsenic trioxide, industrial arsenic compounds, or overdosage by oral administration of inorganic arsenicals produces violent abdominal pains, constriction of the throat, nausea, a marked fall in blood pressure, coma, and prostration. Death may occur within 24 hours, or the individual may partially recover only to succumb within 2 to 4 days from generalized prostration. Water-soluble arsenic compounds are absorbed more readily than insoluble substances, especially those of large particle size.

The odorless and tasteless character of arsenic trioxide permits the ingestion of this substance without suspicion. Accidental or intentional poisoning with "white arsenic" is sufficiently common to warrant toxicologic consideration by the physician, especially when he is presented with a patient suffering from an obscure subacute or severe gastrointestinal upset. A metallic taste with nausea, a burning pain in the region of the esophagus, vomiting, and diarrhea are symptoms suggestive of arsenic poisoning. The odor of garlic on the breath with attacks of vertigo, frontal headache, and muscular cramps may likewise be observed in individuals poisoned with inorganic arsenic compounds. There are many degrees of toxicity, depending upon the amount of arsenic absorbed. In acute cases of poisoning, prostration, coma, and death may ensue within 12 to 18 hours. In most cases of acute fatal poisoning the individual may live for 3 days to 2 weeks.

*Chronic arsenic poisoning.* This type of poisoning with arsenic presents a difficult problem of diagnosis and treatment. Individuals exposed to arsenic in some obscure form may present a puzzling diagnostic picture. Formerly, insecticidal sprays of arsenic compounds frequently caused chronic arsenic poisoning in orchardists and farmers.

Symptoms of chronic arsenic poisoning are vague. A generalized weakness with loss of appetite, nausea, and abdominal discomfort with diarrhea may be experienced. Fleeting pains in the extremities and neuritis may indicate chronic arsenical poisoning of long standing. The mucous membranes of the throat and nose become inflamed with an associated conjunctivitis. One of the diagnostically significant features is brittleness of finger- and toenails and the hair. The skin may become scaly. The palms of the hands and the soles of the feet become hardened and keratosed. A characteristic melanosis of the skin may result. In severe and advanced poisoning, paralysis of the extremities is evident.

Tolerance to the ingestion of arsenic may be developed by repetitious doses over long periods of time. The tolerance may be attributed to an increased excretion rate or diminished absorption owing to the induration of intestinal mucosa.

*Treatment of arsenic poisoning.* Dimercaprol (BAL) is used in the treatment of acute and chronic arsenic poisoning. It is discussed on page 950.

### Bismuth compounds.

The compounds of bismuth of therapeutic importance may be classified in two groups, those employed orally in the treatment of gastric and intestinal irritation and those of chemotherapeutic merit.

**Bismuth Subcarbonate, U.S.P.,** is a white or pale yellowish white powder without odor or taste. It is insoluble in water. This insoluble bismuth compound has superseded bismuth subnitrate in therapy as a gastrointestinal protectant. Bismuth Subnitrate, N.F., is a white powder without odor or taste.

Administered orally, these insoluble preparations are used for their mechanical action as protectives to inflamed or irritated mucous membranes of the gastrointestinal tract. They are administered in finely divided powder form or in suspension so as to favor their distribution evenly throughout the intestinal tract. The bismuth goes into solution to a slight degree, and thus it is said to aid in exerting an astringent and mild antiseptic action. The usual oral dose of these drugs is from 1 to 2 gm. every 2 to 4 hours in the treatment of diarrhea and gastritis.

**Bismuth Subsalicylate, U.S.P.** Formerly bismuth subsalicylate was employed for syphilotherapy. In recent years it has been used as a suppressant for lupus erythematosus. A 10 per cent sterile suspension in oil is injected intramuscularly in doses of 100 mg.

**Bismuth Sodium Triglycollamate, U.S.P. (Bistrimate).** This is a sodium bismuth complex of nitrilotriacetic acid. It is administered orally in tablet form as a suppressant for lupus erythematosus and in lichen planus and scleroderma. Bismuth sodium triglycollamate is usually prescribed in single oral doses of 0.41 gm. (equivalent to 75 mg. of bismuth) 2 or 3 times a day after meals. Higher doses may produce gastrointestinal disturbances.

**Toxicology of bismuth.** Soluble bismuth salts are absorbed from the gastrointestinal tract and will produce bismuth poisoning. The insoluble bismuth preparations may be ingested for long periods of time, and even in the presence of an irritated intestinal mucosa, there appears to be no evidence of toxic effects resulting from their use. In the intestinal tract the nitrate radical of bismuth subnitrate, by the action of fecal organisms, may be reduced to nitrite. Nitrite poisoning has been observed following the therapeutic use of this drug by mouth.

In parenteral systemic therapy the risk of cumulative toxicity from bismuth compounds is obvious. The toxic symptoms produced by bismuth are similar to those of mercury poisoning. The most common sign of bismuth intoxication is renal irritation as revealed by proteinuria. Loss of weight, salivation, and stomatitis may occur in a patient receiving bismuth injections. The bluish black pigmentation which appears on the gums about the base of the teeth is characteristic. Grayish blue areas may also appear on the fauces and soft palate. These discolorations of the oral cavity are believed to be caused by the deposition of bismuth sulfide in the tissue.

Skin lesions may follow the injection of bismuth compounds in some individuals. Pruritus and erythema, urticaria, or dermatitis may occur. Agranulocytosis has been reported following bismuth therapy. The dermatitis of bismuth therapy appears to be analogous to arsenical skin lesions. Other symptoms of toxicity associated with bismuth injections are malaise, nausea, headache, and vague pains in the extremities.

In the event that salivation or stomatitis occurs with the use of bismuth compounds, therapy should be discontinued for a time to permit recovery. Careful attention to oral hygiene on the part of the patient is essential. The administration of the drug should be discontinued at the first sign of cutaneous lesions or albuminuria.

### Antimony compounds.

Historically, the chemotherapeutic success with organic arsenic compounds prompted an examination of the pharmacology of complex organic pentavalent and trivalent antimony compounds. The use of the organic antimonials has been less auspicious in treating diseases. However, they served as the best type of drug therapy available until the sulfonamides and the antibiotics presented a new approach. The trend in therapy is toward the non-metallo organic compounds, even though the organic antimonials are effective agents in some infections states.

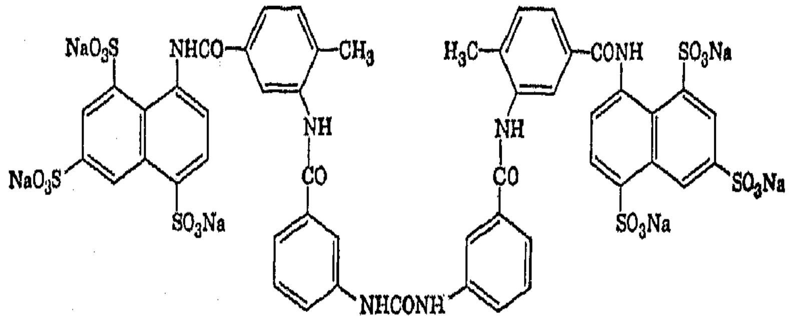
**Antimony Potassium Tartrate, U.S.P. (Tartar Emetic)** ($KOOC\cdot CHOH\cdot CHOH\cdot COO\cdot(SbO)\ \frac{1}{2}H_2O$). This is a white, crystalline compound, soluble in water. This antimony drug is a dangerous but effective agent in *filariasis*, *granuloma inguinale*, and *leishmaniasis*. The dose is 40 mg. administered intravenously as a 0.5 per cent solution 3 times a week. Stibophen is a more satisfactory and less toxic drug.

**Stibophen, U.S.P. (Fuadin).** This antimonial was introduced into therapeutics in the treatment of *lymphogranuloma venereum*. In the molecule, trivalent antimony is combined with pyrocatechin sodium disulfonate. Stibophen is a soluble, colorless, crystalline, odorless powder. It is affected by light. It has been used in the treatment of *granuloma inguinale* and *schistosomiasis*. There is little place for the drug in modern chemotherapy, for the sulfonamide drugs and antibiotics are superior.

### Non-metalloorganic Compounds of Chemotherapeutic Merit

In addition to the sulfonamide drugs and the antibiotics that are used in treating tropical infectious diseases, a number of synthetic organic chemical compounds have been discovered. These drugs are considered in the following section.

**Suramin Sodium U.S.P. (Naphuride, Bayer 205).** Suramin is a urea derivative of the composition shown in the accompanying formula:



Suramin Sodium, U.S.P.

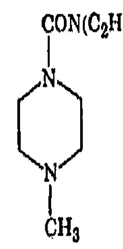
Suramin is a colorless, odorless, tasteless, crystalline compound, readily soluble in water and insoluble in alcohol. The drug is a trypanocide. When injected intravenously, it is slowly eliminated and remains active in the body for a considerable period of time, offering several months' protection against reinfection by trypanosomes of African sleeping sickness. At present the mechanism of action is unknown. Suramin is partially effective in treating adult forms of the filarial worm *Onchocerca volvulus.* It is not as safe as diethylcarbamazine (Hetrazan). However, since no medication is entirely satisfactory in onchocerciasis, suramin is used to a limited degree since it is said to be the only agent which can effect a radical cure of onchocerciasis.

A freshly prepared 10 per cent solution is injected intravenously in doses of 1 gm. weekly until a total dosage of 5 to 10 gm. has been administered. Suramin has been reported to be most effective in the first stage of trypanosomiasis in these doses.

Suramin exerts an irritant action on the kidneys, and after a dose of this drug *albumin, hyaline and granular casts,* and *red blood cells* are frequently found in the urine. In most instances this condition disappears spontaneously within a few weeks. The drug is contraindicated in the presence of kidney disease. Other untoward effects of suramin such as *chills, fever, headache, nausea, pruritus,* and *dermatoses* have been reported.

Patients undergoing therapy with suramin should have daily urine analyses and blood pressure determinations, with frequent blood counts and determination of the blood nonprotein nitrogen content. To detect adrenal cortical damage produced by the drug, frequent determinations of the blood chlorides, potassium, and sodium content are advisable.

**Diethylcarbamazine Citrate, U.S.P. (Hetrazan).** Hewitt and associates (1948), in a study of a group of piperazines for their filaricidal properties, found a compound that possessed marked activity and was deemed suitable for clinical trials. This compound is diethylcarbamazine, 1-diethylcarbamyl-4-methylpiperazine. Diethylcarbamazine citrate is a white crystalline solid, very soluble in water.



Diethylcarbamazine, U.S.P.

Diethylcarbamazine proved to be a significant advance in the chemotherapy of filariasis. As a non-metalloorganic compound it is less toxic than the organic antimonials, the only drugs previously used with success in filariasis. The microfilariae of *W. bancrofti* and *W. malayi* disappear quickly from the blood after therapy with diethylcarbamazine is begun. It is presumed that the adult worms are killed or at least permanently sterilized. The adult forms and the microfilariae of *Loa loa* are killed after several courses of the drug. In *Onchocerca volvulus* infections the microfilariae in the skin are rapidly killed.

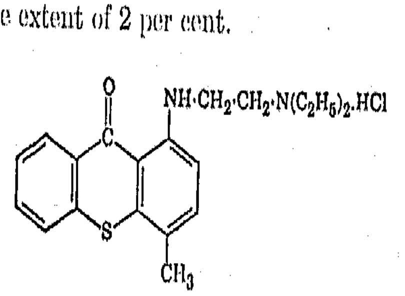
In filariasis diethylcarbamazine in oral doses of 2 mg./kg. 3 times a day for 7 days rapidly reduces the number of microfilariae in the blood.

Toxic effects of the drug, *e.g.,* headache, nausea, sedation, and malaise, are not severe or long-lasting. Fever, leukocytosis, and lymphadenitis are often observed during a course of treatment for filariasis. In acute cases the drug should be given for 3 to 4 weeks.

Hawking and his associates (1955) reported on the mode of action of diethylcarbamazine. They found that the drug had no lethal action on microfilariae *in vitro.* The drug, when administered to experimental animals, produced an accumulation of the microfilariae in the liver, accounting for those that disappear rapidly from the blood. After a period of from 6 to 18 hours the number of microfilariae in the liver diminished, apparently because the parasites have been destroyed. It was concluded that the microfilariae *in vivo* are so modified by the drug that they may be destroyed by the phagocytes of the reticulo-endothelial system. Diethylcarbamazine was found to exert only an insignificant lethal effect on the adult worm *in vivo* and *in vitro.*

**Lucanthone hydrochloride (Nilodin, Miracil D).** In 1948, Kikuth and Gönnert described a new series of compounds belonging to the xanthone and thioxanthone class effective in curing experimental infections of *S. mansoni* in mice and monkeys. These compounds became known as the miracils. Lucanthone is effective in schistosomiasis in a single dose administered orally. Unfortunately, the high incidence of nausea, vomiting, burning sensation in the stomach, and other side effects experienced by patients taking the drug has prevented its widespread use in extensive treatment campaigns. The vertigo, restlessness, tremor, and mental confusion produced by lucanthone is probably related to the nitrogen substituted, phenothiazine-like structure of the drug.

Lucanthone is the hydrochloride of 1-methyl-4-diethylaminoethylaminothioxanthone. It is a finely divided yellow powder, soluble in water to the extent of 2 per cent.



Lucanthone Hydrochloride

Lucanthone is effective against *S. haematobium,* less effective against *S. mansoni,* and of little value against *S. japonicum,* according to Brown (1960) and other workers. It has been used in doses of 0.3 gm. at 12-hour intervals for 5 to 14 days. Some studies in bilharziasis have reported doses of 10 to 20 mg./kg. of body weight for 8 to 20 days.

Hundreds of compounds related to lucanthone have been prepared and tested. None has been found to be superior to lucanthone in man. The unpleasant gastrointestinal effects and the yellow discoloration of the skin severely limit the drug's use (Elslager and Thompson, 1962).

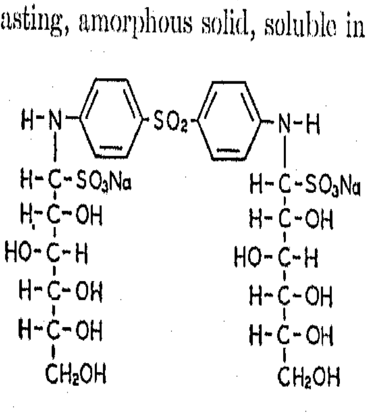
The effectiveness, however slight, of a drug administered by mouth in a disease such as schistosomiasis has served as a great stimulus for future research for a truly curative oral agent.

Lucanthone must be considered as a potentially useful drug. Its low cost is an advantage, but its ultimate place in the chemotherapy of schistosomiasis remains to be established.

### The Sulfones in Leprosy

The synthesis of the sulfone drugs as chemotherapeutic agents in tuberculosis has been mentioned previously. While not sufficiently effective in tuberculosis, these drugs are useful in leprosy. Glucosulfone, sulfoxone, and thiazolsulfone are all used, and there seems to be little preference among the three drugs in leprosy. All are bacteriostatic rather than bactericidal.

**Sodium glucosulfone (Promin Sodium).** This drug is $p,p'$-diaminodiphenylsulfone-N,N'-di-(dextrose sodium sulfonate). It is an odorless, sweet-tasting, amorphous solid, soluble in water.

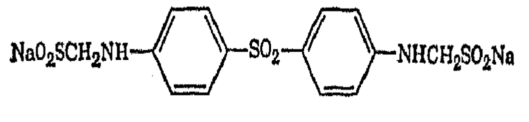


Sodium Glucosulfone, Promin

Sodium glucosulfone is active against the mycobacterium of leprosy.

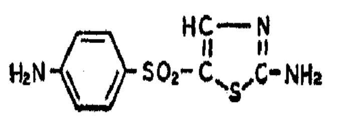
Glucosulfone is administered intravenously in 2- to 5-gm. doses once a day for 2 weeks, followed by a rest period of 1 week before a second course of treatment. The drug is administered for a period of several years.

**Sodium Sulfoxone, U.S.P. (Diasone Sodium).** Sodium sulfoxone is administered orally in the treatment of leprosy. The usual initial dose for adults is 300 mg. daily. If symptoms of toxic effects do not develop (transient normocytic anemia, methemoglobinemia, nausea, hematuria, drug rash, or leukopenia) during the first week, the dose is increased to 600 mg. daily for 2 to 3 weeks. The dosage is gradually increased to 900 mg. daily. This dose schedule may be continued for at least 6 months to evaluate the therapeutic effects.



Sodium Sulfoxone, Diasone Disodium Formaldehydesulfoxylate Diaminodiphenylsulfone

**Thiazolsulfone (Promizole).** Thiazolsulfone is administered orally in 1- to 2-gm. doses 3 times a day.

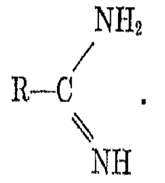


Thiazolsulfone, Promizole 2,4′-Diamino-5-thiazolylphenyl Sulfone

Clinical improvement may be produced by the use of these drugs; however, patients may become refractory, and bacteriologic eradication of the organism is very difficult to achieve. In the opinion of specialists in this field the sulfones are useful drugs, but they have many limitations in the chemotherapy of leprosy. It is possible that control of this disease is intimately linked to the discovery of more effective antituberculosis agents (Douli and Wolcott, 1956).

### Aromatic Diamidines

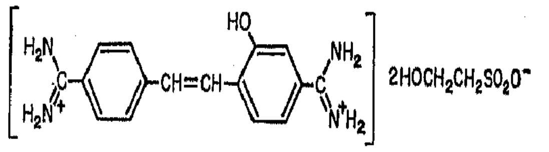
The observation that trypanosomes require glucose *in vitro* for rapid multiplication and motility suggested that hypoglycemic agents may be useful in trypanosomiasis. While insulin proved ineffective, synthalin or decamethylene diguanidine was found to be trypanocidal in rats and active *in vitro*. Thus the protozoicidal action must be unrelated to its hypoglycemic effect in living animals. Lourie and Yorke (1939) investigated the trypanocidal value of the guanidines and diamidine derivatives. It was learned that the guanidine grouping was not essential for trypanocidal activity and that high activity is present in the aromatic diamidines. This latter group of compounds has provided a number of very effective pharmacologic agents possessing the characteristic amidine structure:



$$R{-}C\begin{matrix}\diagup NH_2\\ \diagdown\!\!\diagdown NH\end{matrix} .$$

The drugs of this series that have been studied in human infectious diseases are stilbamidine and hydroxystilbamidine. Another member of this series, phenamidine, is a very effective drug in curing tropical infections in domestic animals. This is of great significance, especially in nations where population demands exceed the food supply.

**Hydroxystilbamidine Isethionate, U.S.P.,** is a yellow, crystalline powder. It is stable in air but decomposes upon exposure to light. It is freely soluble in water. It is 2-hydroxy-4,4′-stilbenedicarboxamidine diisethionate.



Hydroxystilbamidine Isethionate, U.S.P.

Stilbamidine was found effective in North American blastomycosis, certain forms of leishmaniasis, and African trypanosomiasis. Hydroxystilbamidine is equally effective, but it apparently does not produce the delayed trigeminal neuropathy that followed the use of stilbamidine. For this reason hydroxystilbamidine is the drug of choice (Sutliff *et al.*, 1954).

Special precautions are necessary in preparing the solution of the drug for injection. The solution decomposes when exposed to heat, sunlight, or ultraviolet light, forming toxic products. Patients are instructed to avoid extreme exposure to direct sunlight immediately after injections and during a course of therapy. Toxic products may be formed from the action of sunlight on deposits of the drug in the skin.

Delayed toxic effects from hydroxystilbamidine have not been reported. Immediately after an intravenous injection of the drug the blood pressure may fall and the typical histamine responses of tachycardia, flushing of the skin, sweating, salivation, nausea, vomiting, dizziness, dyspnea, and fainting may follow. These may be related to improper preparation of the solution or a too rapid injection rate. The effects usually are transitory and disappear within 15 to 30 minutes. The drug should be administered with caution in the presence of hepatic or renal disease.

The usual dose of hydroxystilbamidine isethionate is 150 mg. for adults administered as a slow, intravenous drip diluted with 200 ml. of 5 per cent dextrose solution or isotonic sodium chloride solution. A second injection is given 24 to 48 hours later. These doses are repeated during a course of therapy for weeks to months, depending upon the nature of the disease and the clinical response of the patient. The special instructions supplied with the drug must be followed exactly to avoid serious complications during therapy.

Hydroxystilbamidine isethionate has been most successfully used in the eradication of the severe pulmonary and systemic infections of North American blastomycosis. It is effective in visceral leishmaniasis (kala-azar) and in actinomycosis, although the antibiotic drugs are much safer. Hydroxystilbamidine may be used in those patients with actinomycosis who have not responded to antibiotic therapy. Unfortunately, this drug is of no value in torulosis or histoplasmosis.

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# 13

# *The Chemotherapy of Amebiasis*

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## PUBLIC HEALTH ASPECTS OF AMEBIASIS

Amebiasis is an infectious disease in which human tissues are invaded by the protozoal ameba, *Entamoeba histolytica*. Included in the clinical term amebiasis are *amebic colitis*, *amebic dysentery*, and *amebic hepatitis*. There is a diversity of opinion regarding the role played by *E. histolytica* in the etiology of amebiasis. *E. histolytica* apparently may live in "carriers" without producing gross symptoms of disease. The apparent symbiosis of amebae and bacteria within the intestinal tract and its relationship to pathogenicity are not understood. In addition, the diagnosis of amebiasis may require careful laboratory investigation and skilled interpretation. The disease is not a simple infection of the intestinal tract or extraintestinal tissues caused by an invading pathogen which can be easily eradicated by chemotherapy.

Amebiasis, while quite prevalent in tropical regions, is not a tropical disease. It has been estimated that in the United States from 5 to 10 per cent of the population pass *E. histolytica* in their stools. This does not mean that from 5 to 10 per cent of the population has amebiasis. Although the incidence of infection is high in rural areas and in chronic hospital patients, in many regions the infection rate is less than 1 to 4 per cent. Amebiasis is more commonly found in the southeastern coastal portion of the United States. The New England states have the lowest incidence. Warm climates favor the persistence of the cysts outside the human host and thus may account for the higher incidence of the disease in tropical and semi-tropical regions. Amebiasis is a serious problem in patients in mental institutions. Among such institutional groups the infestation rate may exceed 50 per cent.

The study conducted by Burrows (1961) indicated that amebiasis is not as prevalent in North America as had been estimated in some previous reports. Burrows concluded from 166 published papers (1945 to 1960), representing nearly one-quarter million persons in the United States and Canada, that about 1 per cent or less of the population of Alaska and Canada and less than 5 per cent of the United States population harbor *E. histolytica*. The higher estimate may be explained by a failure of the laboratory technicians to differentiate *E. hartmanni*, *E. polecki*, and *E. histolytica* from each other (Magath, 1960). In addition, many surveys have been concerned exclusively with hospital populations rather than with general population groups who are less likely to be infected. The accuracy of the diagnosis of amebiasis is not high, according to Shookhoff (1962).

### The Nature of Amebiasis

There are many ways by which humans acquire or transmit this infection: direct contact with the unwashed hands of a "carrier" or a convalescent, ingestion of food or drink contaminated by "carriers," transmission by flies carrying the cysts on their legs or in their excreta, or by ingestion of uncooked food contaminated by contact with soil fertilized with human excreta. Although *E. histolytica* is transmitted only when a susceptible individual ingests the cysts, there are many unanswered questions concerning the pathways available for such transfers. The virulence of the organism varies in different geographic regions, and the degree of susceptibility to infection by the person is influenced by his diet and nutritional status.

Modern public health hygiene has done much to reduce the incidence of amebiasis. Even in semi-tropical areas, improved sanitation for the native population will lower the incidence of amebiasis to a level equal to that found in modern urban communities.

*Entamoeba histolytica* exists in two stages: the active or vegetative stage known as the *trophozoite*, and the inactive or resistant stage known as the *cyst*. The trophozoite moves about and reproduces. This stage is very sensitive to temperature changes, is affected by normal digestive juices, and is not very highly infective. The cyst stage is much more resistant. It may survive outside the body, and normal digestive juices of the stomach do not affect it. Boiling water will destroy the cyst form.

Infected individuals may harbor the parasite and remain asymptomatic. The trophozoite stage obtains its nourishment from the fecal mass and multiplies. If bowel activity is normal, the trophozoite can pass into the cyst stage before it is eliminated in the formed stools. Such an individual then becomes a "carrier." If the trophozoite invades the bowel wall, ulceration and dysentery will result, and the trophozoite will invade the blood stream and be carried to other parts of the body. In such an individual the fecal elimination will be liquid and generally will contain trophozoites rather than cysts. The carrier, excreting the cysts without symptoms of diarrhea, thus becomes the more dangerously infective individual.

Dysentery is only one symptom of the disease. Abscess formation in the liver, lungs, or brain may result from the invasion of the tissues by the motile forms of the *Entamoeba*.

Two "races" of *E. histolytica* may be recognized. The principal distinguishing feature between them is the size of the cysts, from large race cysts greater than 10 micra in diameter to small race cysts less than 10 micra in diameter. It appears that the small variety is far less pathogenic in man and is the amebic infection frequently found in the United States. In addition to this distinguishing feature, strain differences in invasiveness and virulence are encountered clinically. According to Brooke (1958), the so-called small race *E. histolytica* is a separate species, *E. hartmanni*.

The nature of amebiasis, its diagnosis, laboratory identification, sanitary and public health aspects, and epidemiology have become a matter of concern in recent years. In the United States the expanding population and increased soil pollution in suburban communities has intensified the need for improved bacteriologic methods and epidemiologic control. The need for adequate drug therapy is obvious.

An excellent review of the historical aspects of the identification of the pathogenic varieties of amebae and modern technics for the identification of *E. histolytica* is given by Sterman (1962). The application of staining technics and the use of immunologic methods, including the fluorescent antigen-antibody histochemical technic, have helped resolve many of the diagnostic problems of amebiasis.

#### Morphologic differentiation of *Entamoeba* species.

According to Burrows (1959), *E. hartmanni* is generally reported as the "small race of *E. histolytica*," and this accounts for the reported abnormally high incidence of *E. histolytica* in the United States. *E. polecki* is frequently reported as the "large race of *E. histolytica*."

"Hematoxylin staining is the most accurate technic for differentiating *E. hartmanni* and *E. polecki* from *E. histolytica*.

"*Entamoeba hartmanni* may be distinguished from the dwarf forms of *E. histolytica* by the smaller sizes of the trophozoites; by the smaller and more *E. coli*-type of nucleus; by the smaller sizes of the cysts; by the smaller … (ratio) of nuclear diameter to cyst diameter; and by the diffuse type of cyst vacuolation.

"*Entamoeba polecki* may be distinguished from the larger *E. histolytica* by the more variable nuclear structure of trophozoites and cysts; by the frequently darker nucleoplasm; by the predominately uninuclear type of cyst; by the smaller … (ratio of the) nuclear diameter … (to the) cyst diameter; by cytoplasmic condensations and inclusion masses; and by the diffuse type of cyst vacuolation."

### Drugs used in the Treatment of Amebiasis

Several types of drugs have been used in the treatment of amebiasis. Historically, emetine was the first effective drug. The pentavalent and trivalent arsenicals enjoyed a wide use for many years. The halogenated oxyquinolines were introduced as less toxic amebicides and are still used extensively. The discovery of the value of chloroquine in extraintestinal amebiasis opened the way to a new group of drugs, the 4-aminoquinolines, in the treatment of these serious sequelae of intestinal amebiasis. In very recent years the antibiotics have been employed in intestinal amebiasis with successful results.

Opinions differ concerning the merits of the different drugs in amebiasis. The best clinical results seem to have been obtained by the judicious use of several drugs. Therapy is designed to rid the body of the organism and to relieve the symptoms of the disease.

Some studies have been conducted to determine the value of drugs as prophylactic agents in persons exposed to viable cysts of *E. histolytica*. With increased travel to the many areas of the world lacking good sanitary control measures, there is a definite need for prophylactic drugs effective against amebiasis (Beaver *et al.*, 1956).

### Pharmacologic Action of Emetine

The alkaloids *emetine* and *cephaline* occur in ipecac root (*Cephaelis ipecacuanha*) and along with other alkaloids constitute about 2 per cent of the dried root. Emetine hydrochloride is used in the treatment of extraintestinal amebiasis. Emetine is a toxic drug, and its use in the treatment of amebiasis decreased with the discovery of the value of the antimalarial chloroquine in extraintestinal amebiasis in 1948. However, emetine is still employed in amebiasis therapy. Historically, the chemotherapeutic value of emetine in amebic dysentery is chronologically similar to the use of quinine in malaria. Vedder (1912) first demonstrated the virtues of the alkaloid emetine in amebiasis.

#### Absorption and fate of emetine in the body.

Extractive preparations of ipecac root are known to produce emesis. Syrup of ipecac is used to induce vomiting in cases of suspected poisoning. Emetine may be considered the active alkaloid, and when the extractive preparation of the root or the pure alkaloid is administered orally, nausea and vomiting are produced.

In amebiasis emetine is injected subcutaneously. The drug is excreted from the circulation into the intestinal tract, but its emetic action must be considered to reside in the central nervous system. In amebiasis therapy a balance must be achieved among the emetic dose, an effective therapeutic tissue concentration, and the toxic effects on the myocardium. Intravenous injections are contraindicated because they cause marked depression of cardiac muscle. Emetine is slowly excreted from the body.

Experiments *in vitro* have indicated that emetine is toxic to *E. histolytica* in dilutions of 1:5 million. In patients receiving emetine therapy, apparently tissue concentrations of this magnitude or greater are reached. Despite the amebicidal power of emetine *in vitro*, it is generally agreed that the alkaloid does not *cure* more than 10 to 15 per cent of the patients so treated. Emetine apparently interferes with the multiplication of the ameba in its motile vegetative form.

Emetine is retained in the tissue of mice or rats for periods of several months. Two hours after the intraperitoneal injection of the drug, the concentrations have been reported to be highest in the liver, with appreciable amounts in the lung, kidney, and spleen. The concentrations in the brain, muscle, and blood are relatively low. In spite of the high cardiac toxicity of emetine, the concentrations in the heart are also low. The tendency of emetine to concentrate in the liver may explain why the hepatitis of amebiasis is controlled by this drug.

### Emetine Hydrochloride U.S.P.

In amebiasis emetine is administered by deep subcutaneous injection in the form of the hydrochloride, in doses of 1 mg./kg. of body weight over a period of 5 days. It is customary practice to administer subcutaneous 1-ml. doses of 60 mg. per day to adults. The dosage schedule is usually arranged so that not more than 5 daily doses are administered. The drug is not given to children under 8 years of age. For older children and young adults the dose is generally reduced proportionally. Patients should be hospitalized during therapy, and a course of treatment should not be repeated within 30 days. At the present time some authorities feel that the use of emetine should be limited to cases of amebic hepatitis refractory to chloroquine therapy.

Emetine has been found to relieve the symptoms in approximately 85 per cent of patients suffering from acute extraintestinal amebiasis. The drug is most effective against the motile forms of the organism; concentrations necessary to kill the cystic forms cannot be tolerated in man. Relapse is the rule rather than the exception when emetine is used alone in the treatment of amebiasis. Higher dosage levels and longer durations of treatment do not obviate relapse. Repeated periodic courses of treatment with emetine are not advisable. First, they are likely to produce injury to the heart, and second, there is a possibility of the development of drug-resistant strains of the organism. Carbarsone or one of the halogenated hydroxyquinolines is administered concomitantly with emetine to kill the encysted forms of the organism.

Chloroquine has largely replaced emetine as the drug of choice in the therapy of amebic hepatitis.

### Toxicology.

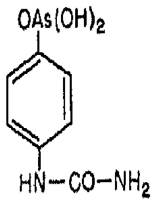
Amebiasis therapy must be intense and of short duration. Prolonged administration of emetine produces nausea, diarrhea, a rapid, irregular, and weak pulse, asthenia, and peripheral neuritis. Deaths have been reported from myocarditis and auricular fibrillation. Idiosyncrasy to the drug is known. If toxic signs appear during therapy, the administration is discontinued. An increase in pulse rate and a lowered blood pressure indicate toxicity to the cardiac muscle. The cardiac toxic effects of emetine can be shown by electrocardiographic studies. Changes in the electrocardiogram have been found 2 years after the therapeutic use of this drug in certain patients.

## ARSENICAL AMEBICIDES

Organic arsenic compounds are effective chemotherapeutic agents in amebiasis. In general, the trivalent arsenic compounds are more effective but also more toxic than pentavalent compounds (Anderson *et al.*, 1949). The theory has been held for many years that protozoa contain and are dependent upon smaller amounts of —SH groups in their enzyme systems than mammalian tissue cells. Organic arsenicals, especially trivalent arsenic compounds, combine with these functionally important sulfhydryl groups and thus destroy the protozoa. Carbarsone and glycobiarsol are pentavalent arsenicals, while arsthinol is a trivalent arsenical. One finds it difficult to reconcile the sulfhydryl binding concept with the effectiveness of the iodinated hydroxyquinolines and the antibiotics in amebiasis. Presumably, these drugs act through other mechanisms to inhibit *E. histolytica.*

### Carbarsone, U.S.P.

The drug is a white, odorless powder, insoluble in water. The tablets and suppositories are official. It is an organic pentavalent arsenical, *p*-ureidobenzenearsonic acid.



Carbarsone, U.S.P.

Carbarsone is used for the treatment of intestinal amebic dysentery. It is effective against both the motile and cystic forms of *E. histolytica.* Orally the usual dose for adults is 0.25 gm. 2 to 3 times a day for 10 days. A retention enema of a solution containing 2 gm. of carbarsone in 200 ml. of warm 2 per cent sodium bicarbonate is employed as supplementary therapy. A rest period should follow a course of therapy with this drug before additional doses are administered.

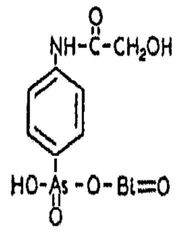
**Absorption and toxicology.** Carbarsone is slowly absorbed from the alimentary tract. The compound is slowly excreted by the kidney. Because repetitious treatment is indicated in amebiasis and because excretion of this drug is prolonged, suitable rest periods must be interposed to prevent toxic effects. While serious untoward effects are rare, cutaneous lesions, fever, epigastric burning, increased intestinal motility, and abdominal pain may occur during therapy. Carbarsone should not be given to patients with liver or kidney disease.

Radke and Baroody (1957) conducted a survey of toxic reactions to carbarsone. They describe 45 cases of toxicity of some form in 1500 patients treated for amebiasis. Nausea and vomiting were most frequently noted, 3 patients developed exfoliative dermatitis, 5 experienced some central nervous system effects, and liver damage was a further complication in one patient. In general, carbarsone is considered as one of the safest arsenical drugs, but it must be used with due care and administered under medical observation.

Carbarsone has been used with success in the treatment of *Trichomonas vaginalis* vaginitis. For this use the drug is incorporated in a suppository in 120-mg. quantities with a glycero-gelatin base.

### Glycobiarsol, U.S.P. (Milibis).

Glycobiarsol is a pentavalent arsenical combined with the metal bismuth. It is bismuthyl-N-glycolylarsanilate having the structure shown in the accompanying formula.



Glycobiarsol, U.S.P.
Milibis

Glycobiarsol is a light pink powder, insoluble in water and soluble in dilute hydrochloric acid. The insolubility of glycobiarsol makes it possible to maintain an effective high concentration of the drug in the lumen of the large intestine. It is said to have more than 10 times the margin of safety of carbarsone.

Glycobiarsol is amebicidal in dilutions of 1:30,000 for *E. histolytica* in an egg infusion medium. In the intestinal tract this drug is slowly and very incompletely broken down so that it is not acutely toxic. Studies on patients have shown that only 2 to 4 per cent of the total dose of arsenic in the molecule is excreted in the urine.

Berberian *et al.* (1952) studied the clinical effectiveness of glycobiarsol in intestinal amebiasis. They compared this drug with other amebicides in subacute and chronic cases. Glycobiarsol was found to be effective in eliminating *E. histolytica* from the intestinal tract in a high percentage of patients over a 2-year observation period. Other workers have reported similar satisfactory results in cases of chronic intestinal amebiasis. Glycobiarsol is very effective in chronic intestinal amebiasis when given orally in 0.5-gm. doses 3 times a day for 8 days. In long-term follow-up studies a high percentage of patients were presumably cleared of the infection. The absence of side effects during treatment is noteworthy. Some workers have found glycobiarsol less effective than the antibiotics in intestinal amebiasis. It is not used in extraintestinal amebiasis.

**Dose.** The average adult dose for a single course of treatment for intestinal amebiasis is one 0.5-gm. tablet orally 3 times a day for 7 to 10 days. This course of treatment may be repeated if positive stool findings persist. Because of potential toxicity, the drug is not administered for periods longer than 1 month. Glycobiarsol is not acutely toxic, but the drug may produce reactions in patients hypersensitive to arsenicals. Cases of arsenical encephalitis and exfoliative dermatitis have been reported after the administration of glycobiarsol. The drug is poorly absorbed from the gastrointestinal tract and, indeed, may produce a marked reduction in peristalsis. This latter effect is likely related to the bismuth in the molecule.

The daily administration of 250 mg. of glycobiarsol provided effective prophylaxis against amebiasis in volunteers periodically challenged with doses of viable cysts of *E. histolytica* (Beaver *et al.*, 1956).

### Combined drug therapy.

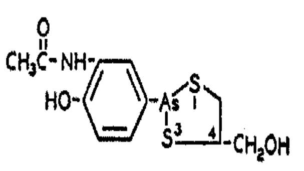
Berberian and his associates (1952) reported the results of their findings on the use of glycobiarsol and chloroquine in the treatment of intestinal and extraintestinal amebiasis. In institutionalized persons exposed intensely to a known reservoir of infection, these drugs were very effective in reducing the reinfection rate. The administration of 0.25 gm. of glycobiarsol and 0.075 gm. of chloroquine phosphate per day for 7 days was rapidly effective in producing stools which were negative for cysts of *E. histolytica* in at least 93 per cent of the subjects. They concluded that the chemoprophylaxis of amebiasis by the simultaneous administration of these two drugs was feasible.

Sanchez Vegas (1953) found a combination of

0.5 gm. of glycobiarsol and 0.15 gm. of chloroquine the most effective amebicide in an extensive study of a number of drugs in this disease. This combined dose was administered twice daily for 15 days. There were few side effects, and these were mild and did not necessitate the interruption of treatment. Silva *et al.* (1958) found similar results after treating patients with glycobiarsol and tetracycline or chloroquine.

**Arsthinol (Balarsen).** A cyclic arsenical compound prepared by combining the arsenoxide form of acetarsone and dimercaprol (BAL) yielded a new type of thioarsenical. This drug, named arsthinol, mercaptoarsenal, or Balarsen, was introduced for the treatment of yaws. It was observed that patients suffering from yaws and infected with *E. histolytica* were rapidly cured of their intestinal amebiasis by arsthinol therapy.

Arsthinol is a trivalent arsenical intended for oral administration in the treatment of intestinal amebiasis. It is 2-(3′-acetamido-4′-hydroxyphenyl)-1,3-dithia-2-arsacyclopentane-4-methanol, as shown in the accompanying formula.



Arsthinol

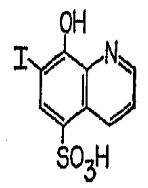
Arsthinol is a white, microcrystalline powder, only very slightly soluble in water or ether. It is soluble in alcohol to the extent of 2.7 per cent.

The drug is administered in intestinal amebiasis orally in courses of treatment lasting 5 days. The daily oral dose is 10 mg./kg. of body weight. The maximal dose in a 24-hour period should not exceed 500 mg. A single dose in the form of a tablet is usually given after the morning meal. Tablets containing 100 mg. of arsthinol are available. Arsthinol may cause toxic effects similar to other arsenicals.

### Halogenated Hydroxyquinolines as Amebicides

**Chiniofon, N.F. (Yatren, Anayodin, Quinoxyl).**

Chiniofon is a mixture of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, its sodium salt, and sodium bicarbonate.

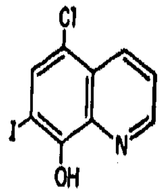


Chiniofon, N.F.

It is a yellow, bitter, soluble powder. This organic iodine compound is effective against both motile and cystic forms of *E. histolytica* but is active only against organisms present in the intestinal tract. It is usually administered in the form of 0.25-gm. enteric coated tablets. The adult dose is 3 to 4 tablets 3 times a day by mouth, administered for from 7 to 14 days. The drug does not produce toxic symptoms when used in therapeutic doses. Chiniofon should not be used in the presence of liver damage and must be administered cautiously to patients with thyroid disease or iodine intolerance.

**Iodochlorhydroxyquin, U.S.P. (Vioform).**

Iodochlorhydroxyquin is 5-chloro-7-iodo-8-hydroxyquinoline.



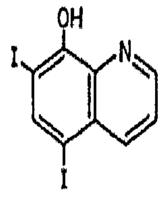
Iodochlorhydroxyquin, U.S.P.
Vioform

This drug is a brownish yellow, insoluble powder. Iodochlorhydroxyquin is administered orally in the form of 0.25-gm. tablets. From 3 to 4 tablets per day for 10 days is considered a course of treatment. Gastrointestinal irritation may be produced by iodochlorhydroxyquin. The drug should be administered with caution in cases of liver damage. After a course of therapy, 7 to 10 days should elapse before the drug dosage is repeated.

**Diiodohydroxyquin, U.S.P. (Diodoquin).**

Diiodohydroxyquin is a yellowish brown powder, almost insoluble in water and sparingly soluble in alcohol. The compound is an amebicide and protozoacide of low toxicity. It is 5,7-diiodo-8-hydroxyquinoline.

Diiodohydroxyquin is a relatively nontoxic compound. Clinical studies with this drug indicate that it is effective in intestinal amebiasis. It is administered orally in the form of tablets, 650 mg. 3 times a day for 7 to 20 days. Diiodohydroxyquin has been used prophylactically in amebiasis in doses of 650 mg. once a day.



Diiodohydroxyquin, U.S.P.
Diodoquin

### Dichloracetamides as Amebicides

Several drugs of this class of compounds have been developed mainly for the treatment of chronic intestinal amebiasis. They do not appear to be of value in treating hepatic amebiasis.

**Chlorbetamide (Mantomide).**

This drug is dichloro-N-(2:4-dichlorobenzyl)-N-(2-hydroxyethyl)-acetamide. It was developed by Dennis and Berberian (1954). The effectiveness of chlorbetamide in treating *E. histolytica* infection in hospitalized, chronically ill schizophrenic patients has been demonstrated (Vestergaard *et al.*, 1958). It has not been shown that other amebicides would be equally effective.

In the experimental study in psychiatric patients, 750 mg. of chlorbetamide was administered orally 3 times daily for 1 week. Repeated courses of treatment were instituted as required. Untoward reactions attributed to the drug were mild and rarely observed. The significance of amebiasis in mental hospitals is reviewed by these authors, and the difficulties of treating the entire hospital population are stressed. This report is typical of the medical problems associated with the control of amebiasis by drug therapy in hospital patients.

### Drugs Used in Extraintestinal Amebiasis

**Chloroquine Phosphate, U.S.P.**

Chloroquine was introduced as an amebicide by Conan (1948). Conan reasoned that the antiamebic property of the halogenated hydroxyquinolines might reside in the quinoline portion of the molecule. Therefore he tried the antimalarial drug chloroquine, which is a 4-aminoquinoline. The early clinical experiences with this drug in amebiasis met with conspicuous success. These findings have been amply confirmed. Hydroxychloroquine and amodiaquin are fully as effective as chloroquine in hepatic amebiasis, according to some authors.

Chloroquine is almost completely absorbed from the upper intestinal tract, and it is slowly excreted. Its important characteristic is that it is concentrated inside various cells, especially the liver cells. This is thought to be significant in cases of hepatic amebiasis. A number of reports have appeared describing the efficacy of chloroquine therapy in hepatic amebiasis. However, Beaver *et al.* (1956) did not find chloroquine or quinacrine effective as prophylactic drugs in experimental intestinal amebiasis in human volunteers.

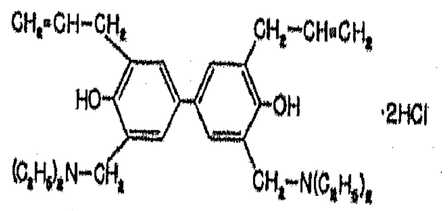
**Dose.** Chloroquine has largely replaced emetine as the drug of choice in the therapy of amebic hepatitis. The initial oral dose of 1 gm. of the phosphate is given for 2 days. Thereafter 0.5 gm. is administered daily for 14 days. A second course of treatment may be given if necessary.

Chloroquine therapy is a significant advance in the treatment of amebiasis. It is inexpensive, active orally, devoid of untoward side effects, and comparatively nontoxic.

Chloroquine is not concentrated in the tissues of the large intestine, and it is not effective in intestinal amebiasis. For this reason it is necessary to use one of the chemotherapeutic agents active against the intestinal forms in combined therapy with chloroquine. Apparently *E. histolytica* does not develop resistance to chloroquine, so that the drug may be used routinely in individuals with suspected extraintestinal amebiasis. In cases in which the diagnosis is not positive, the symptoms may rapidly disappear after the drug is administered in a course of therapy if they were related to amebic liver involvement.

**Bialamicol (Camoform).**

Bialamicol (6,6′-diallyl-α,α′-bis-(diethylamino)-4,4′-bi-*o*-cresol dihydrochloride) is an orally effective amebicide active against intestinal forms of amebiasis.



Bialamicol Hydrochloride
Camoform

Thompson (1959) reported that bialamicol was effective *in vitro* against *E histolytica*, and active in animals experimentally infected with *E. histolytica*. Prophylactic oral administration of the drug conferred significant protection against hepatic and pulmonary amebiasis in hamsters. The ability of the substance to be stored in various tissues of experimental animals suggested the probable usefulness of bialamicol in extraintestinal amebiasis. The drug is relatively nontoxic and is absorbed from the gastrointestinal tract.

Preliminary clinical trials with bialamicol indicate that the drug is effective in intestinal amebiasis, and it may be of value also in the treatment of extraintestinal infections. In adults, oral doses of 250 to 500 mg. (1 to 2 tablets) 3 times daily with meals is the suggested regimen of therapy for 5 days. Patients not cured of the infection by this course should have a 3-week rest period before treatment is repeated.

Bialamicol is well tolerated; gastrointestinal distress with nausea and vomiting seem to be the chief untoward effects following oral doses. Skin reactions including exfoliative dermatitis have been reported. In these cases the drug should be discontinued. If further clinical experiences support the present findings, bialamicol will be a unique amebicidal drug, active against both intestinal and extraintestinal forms of the disease.

### ANTIBIOTICS IN AMEBIASIS

Clinicians have observed that the administration of sulfonamides or penicillin to patients with amebic colitis frequently improves the course of the infection, despite the persistence of *E. histolytica* in the stools. The role of the normal intestinal bacteria in amebiasis is not understood. In fact, the significance of the enteric flora in the pathogenesis of amebiasis is debatable. *In vitro* it is difficult to maintain cultures of *E. histolytica* without living bacteria, bacterial filtrates, or protozoa in the culture medium (Rees, 1955).

In a study of the effect of antibiotics on the *in vitro* culture of *E. histolytica*, Balamuth (1955) revealed that a well-controlled *in vitro* test is useful in a drug screening program. On the basis of such experiments fumagillin was found to be the most promising antibiotic active against *E. histolytica*. Oxytetracycline is highly effective against intestinal amebiasis, as is chlortetracycline, paromomycin, and erythromycin. Oxytetracycline appears to be superior. These antibiotics are not effective in hepatic amebiasis.

There have been numerous clinical reports on the satisfactory use of the broad-spectrum antibiotics and fumagillin in amebiasis. The broad-spectrum antibiotics destroy the bacteria in the bowel, in addition to their effect upon the ameba. Fumagillin is without activity against the normal bacterial flora of the gastrointestinal tract.

Despite the *in vitro* activity of fumagillin and its effectiveness in experimentally infected animals, which exceeds all other drugs including emetine, the antibiotic is not superior in man to the broad-spectrum antibiotics in clinical effectiveness. Large doses of any of these antibiotics in amebiasis may produce untoward effects. In addition, the antibiotics may have only a temporary effect. With a gradual return of the flora of the gastrointestinal tract and a return of the ameba, relapse will frequently follow (Anderson, 1960).

Comparative studies with oxytetracycline, chlortetracycline, chloramphenicol, erythromycin, and bacitracin indicate that there is much to be learned about the place of these drugs in the treatment of intestinal amebiasis. Some workers could not detect any significant difference in the parasitologic or clinical response between oxytetracycline and fumagillin. Brown and his associates (1956) reported that fumagillin was the most promising of the antibiotics, with minimal side effects. Other workers have combined the use of an antiboitic and chloroquine or carbasone, depending upon the character of the infection.

Oxytetracycline has been employed, 0.5 gm. every 8 hours for 10 days, and chloroquine, 0.3 gm. twice daily for 7 days, either concurrently or sequentially. The advantage of this plan of treatment is its simplicity, low relapse rate, and low cost. Frye (1952) reported that oxytetracycline in doses of 2 gm. daily for 10 days produced a cure rate of 97 per cent with a low relapse rate. Chlortetracycline produced a cure rate of 70 per cent with a higher relapse rate.

### Paromomycin (Humatin).

This antibiotic, active against *Salmonella*, *Shigella*, *E. coli*, *Proteus*, *Aerobacter*, and staphylococci, is effective in doses of 10 to 20 mg./kg. of the base for 14 days in amebic dysentery (Shafei, 1950). The sulfate salt is poorly absorbed from the gastrointestinal tract and is well tolerated. The clinical experience with this salt of paromomycin suggests that it is useful in the treatment of acute and chronic intestinal amebiasis (Courtney *et al.*, 1960). The place of the antibiotic in amebiasis therapy remains to be established.

### Fumagillin (Fumidil).

Fumagillin is a crystalline antibiotic elaborated by a strain of *Aspergillus fumigatus*. It was first described in 1949 by Hanson and Eble. Its empirical formula is $C_{27}H_{36}O_7$. It is insoluble in water and partly soluble in chloroform. This antibiotic is a direct-acting amebicide. It has no anti-bacterial spectrum and thus is a specific drug for intestinal amebiasis.

Anderson and his associates (1960) found fumagillin to be effective *in vivo* in experimental *E. histolytica* infections in monkeys when administered orally. Later they proved the antibiotic to be active in amebiasis in man.

Following 60-mg. oral daily doses of fumagillin, side effects have been transient but occasionally have required withdrawal of the medication. Nausea, anorexia, occasional vomiting, increased frequency of stools, and mucocutaneous reactions have been reported. With larger doses the side effects are more frequent. A vesicular type of skin eruption followed by mild desquamation has been produced by the administration of fumagillin. A few cases of neutropenia have been described following fumagillin therapy; for this reason peripheral blood cell counts may be a wise precaution during prolonged administration.

**Dose.** The recommended dose of fumagillin is 30 to 60 mg. daily in divided doses, 3 or 4 times a day, for 10 to 14 days. One such course appears sufficient to clear most cases of intestinal amebiasis. Until more clinical experience has been acquired, this dose should not be exceeded.

Because fumagillin is not active against bacteria, it should not produce a change in the normal flora of the gastrointestinal tract. This factor enhances its value in the treatment of intestinal amebiasis, since there is no danger of overgrowth of yeasts and fungi following its administration.

### CHOICE OF DRUGS IN AMEBIASIS

Unless serious complications arise, amebiasis may be unrecognized and the patient will receive only symptomatic treatment. The reported incidence of intestinal and extraintestinal amebiasis varies widely and seems to be dependent upon the thoroughness of the search for the parasite. Therefore unless vague symptoms referable to the gastrointestinal tract are carefully checked, early diagnosis may be impossible, and an infection which might have been rapidly and completely cured can become an incapacitating or even a fatal illness. In addition, the problem of seemingly healthy "carriers" complicates the therapeutic and public health aspects of the disease. No positive statements can be made regarding the accepted superiority of a drug or drugs in the treatment of amebiasis. An attempt has been made in this chapter to present the changing character of the chemotherapy of this disease.

For acute intestinal amebiasis, oxytetracycline and fumagillin are equally effective. In the control of a water-borne epidemic, Sappenfield *et al.* (1955) used these two drugs interchangeably. They are potentially less toxic than other drugs, and in patients not likely to be exposed to reinfection, these antibiotics are useful therapeutic aids. At times emetine may be used in intestinal amebiasis in cases of severe dysentery proving refractory to other drugs; however, the hazards associated with its use must be recognized, and it cannot be expected to clear the intestine of the parasite.

The older amebicides, carbarsone, and the halogenated hydroxyquinolines are less efficient than glycobiarsol or arsthinol. Diodoquin seems to be one of the best drugs available for chronic amebic infections.

As has been stressed, in amebic hepatitis, pneumonitis, skin lesions, and other forms of extraintestinal amebiasis, chloroquine or hydroxychloroquine are the drugs of choice. In these cases combined therapy is advisable, using either an antibiotic or one of the intestinal amebicides. It has been suggested that patients with amebiasis with or without dysentery should be protected against hepatic and pleuro-pulmonary involvement by chloroquine while an amebicide active in the intestine is administered.

The ideal chemotherapeutic agent in amebiasis has not been found, but the increased tempo of activity in this long-dormant area of chemotherapy suggests that agents superior to those now available will be discovered.

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# 14

# *The Use of Drugs in Helminthiasis*

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Parasitic invasion of the human body by helminths constitutes one of the major public health problems of the world. The control of worm infestation is complicated by the living habits of large segments of the world's population, and since social, economic, dietary, and environmental factors play such a prominent role, the problem resembles in many respects the regulation of malaria. It is estimated that approximately 800 million people are suffering from some type of worm infestation. In some tropical areas the extent of worm infestation exceeds 90 per cent, and individuals may be infected with several types of helminths. Of the 500,000 natives of Puerto Rico residing in the United States, Most (1958) estimates that as many as 10 per cent may be infected with *Schistosoma mansoni*. It is certainly reasonable to believe that other forms of helminth infection may be found in these people and other ethnic groups residing in this country. This was demonstrated by Ballinger *et al.* (1962), when they reported a 28.8 per cent incidence of intestinal parasitism among hospital employees in two hospitals in New York City.

It should be emphasized that worm infestation is not restricted to tropical climates. Indeed, trichinosis is a significant health problem among Eskimos and Alaskan Indians in Alaska, where *Trichinella spiralis* is present in a wide variety of wild animals used as food. If 21 million North Americans are estimated to have ingested *T. spiralis* and another 18 million are infected with pinworms, the epidemiology of helminthiasis is important in the United States. With such large numbers of individuals infected, the control of helminthiasis requires special educational measures. Treatment of the disease involves not only a knowledge of the character of the life cycle of the infecting parasite but also suitable ***anthelmintic agents*** and health educational measures.

Table 14-1 lists the worms commonly found in the gastrointestinal tract and other organs of man.

Anthelmintics are drugs used to kill or remove intestinal parasites. Most anthelmintic agents affect the helminths in such a manner that peristaltic activity or catharsis expels the parasites from the intestinal tract. The worms may not be killed by the anthelmintic drug, but this is immaterial if the infestation is cleared.

Extraintestinal invasion of tissues by helminths presents a very difficult therapeutic problem. An effective drug must destroy these invasive parasites without producing toxic effects. Only in re-

TABLE 14-1

*A Classification of the Common Helminths Causing Infestation in Man*

*Nemathelminthes* (nematodes)
  Hookworm
    *Ancylostoma duodenale*
    *Necator americanus*
  Roundworm
    *Ascaris lumbricoides*
  Whipworm
    *Trichuris trichiura*
  *Strongyloides stercoralis*
  Pinworm
    *Enterobius vermicularis*
  *Trichinella spiralis*
*Platyhelminthes*
  Tapeworm (cestodes)
    *Taenia saignata* (beef tapeworm)
    *Taenia solium* (pork tapeworm)
    *Hymenolepis nana* (dwarf tapeworm)
    *Diphyllobothrium latum* (fish tapeworm)

cent years have satisfactory anthelmintics been discovered that appear to be promising as "systemic anthelmintics." An example of this latter class is chloroquine, which is effective in some forms of schistosomiasis. In this chapter those agents which are effective as intestinal anthelmintics will be considered.

An effective anthelmintic drug should meet the following requirements:

1. The drug should reach that portion of the intestine where the worm infestation occurs with a minimal degree of absorption.
2. It should be more toxic to the invading helminth than to the mucous membranes of the gastrointestinal tract.
3. If absorbed from the alimentary tract, the drug's systemic toxicity should be minimal.
4. The drug should be tolerated orally without producing symptoms and should be inexpensive.

Only a few anthelmintic agents meet all of these requirements at the present time.

The anthelmintic drugs are administered during a course of therapy for the control of intestinal parasites. Such a course of treatment involves a preliminary dietary regimen, the use of suitable cathartic drugs, bed rest, and medical supervision. Therapy varies with the nature of the individual drug and the character of the infection. For the details of therapy the student is referred to specialized texts on helminthology.

The diagnosis of infections of parasitic worms is dependent upon laboratory findings. The symptoms are so variable, multiple infection is so frequent, and the clinical picture may resemble so many non-helminthic syndromes that accurate diagnosis requires laboratory tests. A course of anthelmintic therapy should include pretreatment and post-treatment standardized laboratory examinations. Fecal egg counts are of great value in diagnosis. Recovery of expelled worms after treatment will permit an accurate assessment of the success of anthelmintic drugs.

A brief outline of the character of the common helminths and certain of the essential characteristics of their life cycles is described.

## COMMON HELMINTH DISEASES

### Ancylostomiasis (hookworm disease).

Ancylostomiasis is caused by an intestinal infection in man by *Ancylostoma duodenale* or *Necator americanus*. The disease is found in tropical and subtropical countries. Where there is a warm, moist, fecally polluted soil, the infection may be anticipated. The filariform larvae of the worms penetrate the skin upon contact.

The eggs of the worm are excreted in the feces. In a favorable soil environment they hatch within 2 days. After a period of 5 to 6 days, the larval forms become the motile, infective, filariform larvae. After penetrating the skin of man these motile forms enter the lymphatics and small blood vessels. In the lungs they enter the alveoli, ascend the trachea to the throat, and are swallowed. In the small intestine within 4 to 7 weeks the larvae develop into mature worms. The adult worm firmly attaches itself to the intestinal mucosa (fig. 14-1). It is cylindrical in shape and about 10 mm. in length. The head of the worm secretes an anticoagulant substance, and *A. duodenale* passes the blood of the host through its body. Both varieties of worms are believed to secrete a hemolytic toxin that may account in part for the severe anemia of ancylostomiasis. It is estimated that from 6 to 8 weeks elapse from the time the larvae have penetrated the skin until the adult female worms lay eggs that are passed in the feces.

A dermatitis with intense *itching*, *erythema*, *edema*, and a *papular eruption* may develop at the site on the skin where the filariform larvae enter.

The clinical manifestations of the pulmonary involvement resemble those of *ascariasis* but are less severe. In mild intestinal infections the individual may remain asymptomatic. Severe infections result in *indigestion*, *eructations*, *anorexia*, *headache*, and *vertigo*. In advanced cases epigastric pain, and abdominal tenderness develop, with symptoms of chronic fatigue, anemia, mental torpor, and alternating diarrhea and constipation. Positive diagnosis is made by microscopic identification of hookworm in the feces.

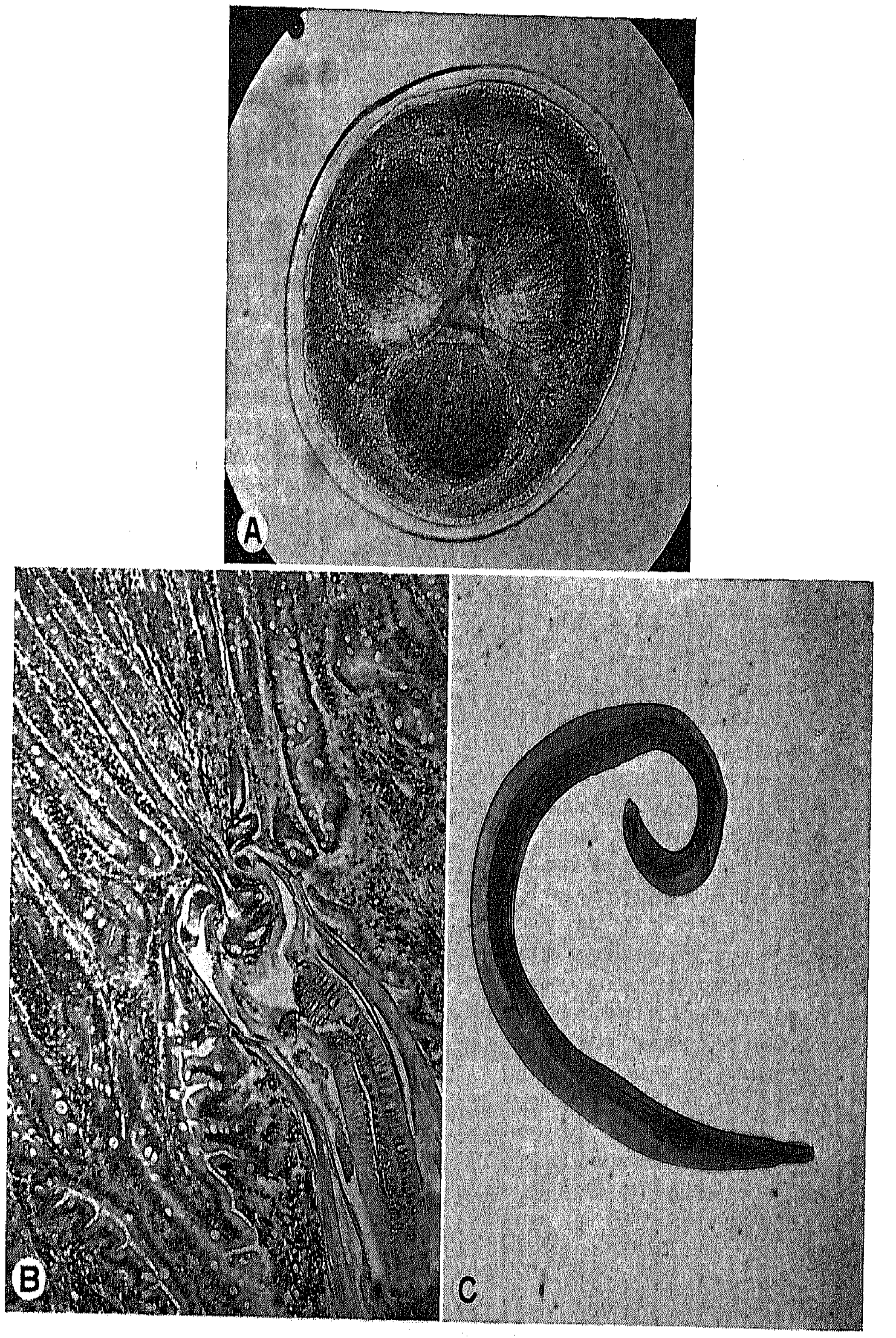


FIG. 14-1. *A*, A head-on view of *Ascaris*. The triangular opening is the mouth, surrounded by three cloverleaf-like lips. *B*, Hookworm in intestinal muscle. *C*, pinworm showing structural details, 2 to 13 mm. in length. Photographs courtesy of Jack Kath of Merck Sharp & Dohme Research Laboratories.

Tetrachloroethylene is the drug of choice in the modern treatment of ancylostomiasis. Bephenium hydroxynaphthoate is an effective agent in hookworm infestation and is also indicated when mixed infections of hookworm and roundworm are present because the drug is active against both parasites. Hexylresorcinol, the cyanine dyes, carbon tetrachloride, and thymol are also employed as anthelmintics in hookworm infestation.

### Ascariasis (roundworm infestation).

Ascariasis is caused by the helminth *Ascaris lumbricoides*. It is one of the most common helminth infections in man. Children are particularly susceptible to ascariasis. The condition is highly endemic wherever soil pollution with human feces occurs. The worms gain access to the intestinal tract directly by ingestion of ova containing viable embryos. The larvae are liberated in the small intestine, penetrate the intestinal wall, and enter the circulating blood stream. The larvae are deposited in the lungs, where many of them penetrate the alveoli. After a period of growth the larval forms migrate up the respiratory passages and are swallowed. The adult worm develops in the small intestine (fig. 14-1). Female ascarids are approximately 20 to 35 cm. long and 3 to 6 mm. in diameter. Male worms are about 15 to 30 cm. long and 2 to 4 mm. in diameter. It is estimated that the period of time elapsing between the swallowing of an ovum and the production of eggs by the adult parasite is from 2 to 2½ months. The infestation may be asymptomatic. Microscopic demonstration of ova in the feces may be required to establish a diagnosis, or the adult worms may be recovered in the fecal discharge. In severe infestation the large numbers of adult worms in the intestine may cause *abdominal discomfort*, *anorexia*, *nausea*, or *colic*. Intestinal obstruction may result from the presence of a mass of worms. Symptoms may be caused by migrating larvae or by the adult worms. The excretions of larval and adult forms of the worm are toxic. For example, extracts of *Ascaris lumbricoides* have been shown to produce anaphylactic-type reactions upon contact with mucous membranes or abraded skin areas.

Piperazine salts are the most satisfactory anthelmintic agents in ascariasis. Hexylresorcinol has been widely used with success in the treatment of roundworm infestation. The recently introduced bephenium hydroxynaphthoate may become the drug of choice in ascariasis. Diethylcarbamazine is also an effective drug. Santonin and oil of chenopodium have also been used as anthelmintics in roundworm infestation, but they are more toxic.

### Trichuriasis (whipworm infection).

Trichuriasis is caused by *Trichuris trichiura*, a common intestinal nematode. Infestation in humans results from the ingestion of ova from fecally polluted soil. Whipworm infestation is found in all parts of the world. It is most prevalent in warm climates. According to some authorities, trichuriasis is the second most common helminth disease in the United States.

In trichuriasis the eggs develop in the upper portion of the duodenum. The motile larvae that are hatched pass into the cecum and attach themselves to the intestinal wall. Adult worms mature within about 3 months' time. In the cecum the adult worms become firmly anchored within the mucosa. The adult worm is thread-like and ranges in size from 30 to 50 mm. in length. The wider posterior portion of the male worm is coiled like a watchspring.

Whipworm infestation may be without symptoms unless the infection is very heavy. In these cases there may be *indigestion*, *mild anemia*, *insomnia*, and *urticaria*. A diagnosis is made only upon demonstrating the characteristic ova in fecal smears by microscopic examination.

Dithiazanine is the drug of choice in the treatment of whipworm infestation. Hexylresorcinol has been used with limited success. Piperazine has been reported to be effective, but some workers have disputed its value.

### Enterobiasis, oxyuriasis (pinworm or threadworm infestation).

Enterobiasis is caused by the nematode *Enterobius vermicularis*, also designated as *Oxyuris vermicularis*. Pinworm, seatworm, or threadworm infestation is most prevalent in children of school age, especially in inmates of institutions. The infection is usually found in all members of a family. The infection is acquired directly by the ingestion of the ova. In the intestine the eggs hatch and release larval forms which mature in the ileum. The fertilized female worm migrates to the perianal area. The mature eggs are deposited in the folds of the anus, vulva, and perianal skin. Female worms measure from 8 to 12 mm. in length; male worms are only 2 to 5 mm. long (fig. 14-1).

The worms cause irritation and secretion of mucus within the intestine. Frequently the worms form small balls. Enormous numbers of ova are passed in the stools. Itching of the perianal region may be the only clinical symptom in cases of light infection. A heavy infestation may cause *anorexia*, *abdominal pain*, *weight loss*, *insomnia*, and *nervousness*. Microscopic identification of the eggs in the feces or from swabs of the anal skin will provide a positive diagnosis. Anal impressions, using cellophane adhesive tape, are made on several successive days to establish a diagnosis.

Piperazine is the drug of choice in enterobiasis. Gentian violet medicinal and the cyanine dyes are also effective. The large number of drugs that have been evaluated in enterobiasis have been reviewed by Bueding and Swartzwelder (1957). Some agents are not used either because they are too costly, are only moderately effective, or elicit undesirable side effects.

The ease with which reinfection is acquired after treatment in pinworm infections often makes a cure doubtful. The presence or the absence of the infection is established with difficulty. The finding of adult worms or eggs may signify an infection that is receding. For these reasons it is generally agreed that eggs must be found on at least 3 examinations before it can be assumed that an infection is present and likely to continue. Others contend that 7 negative examinations are needed before the assumption is made that the infection is absent or has been cleared by drug therapy. These diagnostic and therapeutic problems have undoubtedly complicated the clinical trials of drugs in this infection. Prophylactic suppression, not cure, is generally the aim in treating enterobiasis in children in institutions.

### Strongyloidiasis.

This disease is most frequently acquired by the penetration of the skin by the larva of *Strongyloides stercoralis*, rarely by their ingestion. The larvae invade the blood stream and are carried to the lungs, where they break through into the alveoli. The males and females develop within a few days. After fertilization, the female worm finds its way into the upper intestine by way of the trachea and esophagus. The eggs are deposited in the mucosa of the duodenum and upper jejunum. The eggs are hatched in the tissues of the host, and the motile larvae penetrate the mucosa and are passed in the feces. Within 24 hours in a favorable environment they may develop into the skin-penetrating filariform larvae.

The infection resembles hookworm infestation in many aspects. The larval forms in fresh stools or in aspirated duodenal juice provide a diagnosis and differentiation from hookworm larvae.

Since the infection involves the upper intestinal tract, therapy is difficult. The cyanine dyes, pyrvinium chloride (Vanquin), or dithiazanine iodide (Delvex) are effective. Formerly gentian violet medicinal was used, although complete elimination of the infection was usually not achieved with this drug.

### Trichinosis.

Trichinosis is caused by *Trichinella spiralis* infestation. The disease is particularly prevalent in the United States. The infection is obtained by eating raw or improperly cooked pork containing viable larvae. The larvae pass to the small intestine where they invade the intestinal mucosa. Within a few days they mature into small adult worms. The fertilized female worms burrow into the mucosa and produce large numbers of living larvae. These larvae find their way into the lymphatics and venules and eventually to all parts of the body. Within 8 to 9 days after the initial infection the encysted larvae may be found in striated muscle.

The muscles that have been found to contain the encysted larvae in greatest numbers are the laryngeal, lingual, orbital, abdominal, intercostal, and diaphragmatic.

The means of control of trichinosis have been pointed out by numerous writers. The disease can be eliminated by providing and enforcing regulations to prevent the feeding of raw garbage to swine. The incidence of trichinosis in garbage-fed hogs is more than 10 per cent, while in grain-fed hogs it is less than 1 per cent, and in swine fed cooked garbage, it is negligible. Unfortunately, most communities have been unwilling to enforce such public health regulations.

The symptoms of trichinosis are variable. There may be *nausea*, *vomiting*, *abdominal pains*, *fever*, and *dysentery*. Symptoms of *malaise*, *weakness*, *intermittent fever*, *profuse sweating*, *periorbital edema*, *dermatitis*, and *cardiac* and *respiratory distress* may be associated with the migration of the larvae. The infection can be fatal. The severity of the infection determines in large measure the character of the symptoms. Many infected persons remain asymptomatic. These may be altered by the age and the physical health of the individual. After a period of acute illness which may last for from 1 to 3 weeks, the symptoms gradually subside. Diagnosis is difficult, as the larvae are not observed in the feces, blood, or spinal fluid. The larvae may be identified from muscle biopsies.

The administration of ACTH or cortisone to patients with trichinosis has produced marked improvement of the severe clinical symptoms and eventual recovery. These hormones do not affect the invading parasites but apparently produce an alteration in the body's reaction to the infestation. Much of the clinical picture of trichinosis suggests an antigen-antibody reaction to toxic products or stress. For this reason the corticosteroids may be useful in therapy.

The anthelmintics are valueless in trichinosis. Treatment is symptomatic and is designed to prevent the early migration of the larvae into the intestinal mucosa by catharsis. Piperazine citrate has been shown to be effective against the intestinal phase of trichinosis in mice. Its use is suggested in the partial control of the intestinal infection in epidemics of trichinosis, where an early diagnosis can be made.

### Cestodiasis, taeniasis (tapeworm infection).

Taeniasis is caused by one of three platyhelminths: *Hymenolepis nana*, dwarf tapeworm; *Taenia saginata*, beef tapeworm; and *Taenia* *solium*, pork tapeworm. *Diphyllobothrium latum*, or fish tapeworm, is more common in fresh water fish in Europe than in the United States.

A tapeworm has a scolex, or head, which attaches itself to the small intestine, and a variable number of proglottids, or segments, are formed from the scolex. The segments may break off and others will be regenerated from the scolex; therefore an effective anthelmintic must remove the scolex.

Dwarf tapeworm infestation is frequently found in children in the southern United States. The adult worm is approximately 20 mm. in length, as compared with the other varieties which may be several meters long. Infection usually results from eating food contaminated with viable ova from human feces. There are no characteristic symptoms of the infestation, and as in other helminth infections, the symptoms vary with the degree of infestation. *Abdominal pain, diarrhea, dizziness, headache*, and *nervous disturbances* with *asthenia, anemia*, and *eosinophilia* have been reported. The ova, which are characteristic, may be identified in the stool. Segments of the worm may be expelled.

Beef tapeworm infection may be acquired by eating raw or improperly cooked beef containing a viable, intact *Cysticercus*. Cattle serve as an intermediary host for the worm. They become infected by ingesting human feces containing viable ova from contaminated pastures. The ova hatch in the intestine of this animal and penetrate into the muscle tissue, where they develop into the larval forms or cysticerci. When the meat is properly and adequately cooked, these forms are killed. The mature worm may attain a length of over 10 meters.

Pork tapeworm infestation results from eating raw or inadequately cooked pork containing the cysticerci of the worm. The life cycle of *T. solium* is essentially the same as that of *T. saginata*. In the case of the pork tapeworm, however, the infection may also be acquired by consuming food or water contaminated with viable eggs. The symptoms of pork tapeworm infection resemble those of beef tapeworm infestation.

Human infestation may not be limited to one tapeworm. After ingestion of the cysticerci, the adult worms develop in the small intestine in man. They attach themselves to the intestinal wall and produce leukocytosis with eosinophilia early in the infection. There are no characteristic symptoms. The detection of ova and segments of the worm in the stool is of diagnostic importance. A positive identification of tapeworm infection must be made before treatment is instituted.

Treatment of all types of tapeworm infestation with the anthelmintic drugs is possible. Quinacrine is considered the drug of choice in beef tapeworm and fish tapeworm infections. This drug may produce cysticercosis in *T. solium* infestation, and it is not very effective against dwarf tapeworm. Oleoresin of aspidium and hexylresorcinol have also been used in tapeworm infestations.

## ANTHELMINTICS

### Discovery of anthelmintic drugs.

When one considers the magnitude of helminth infestation in man and animals, it is surprising that chemotherapeutic studies have not developed comparable to those evolved for the other major diseases. The number of effective anthelmintic drugs is small, and there have been few systematic studies of structure-activity relationships of compounds of potential interest. Since 1940 some progress has been made, especially with phenothiazine, piperazine, acridine, and xanthone derivatives. However, as is often the case, an understanding of the mechanism of action and the parasite receptor sites involved is an important prerequisite for the discovery of superior drugs. There is a tragic lack of knowledge of the physicochemical, biochemical, and metabolic relationships to the therapeutic applications of anthelmintic agents.

All of the available anthelmintic drugs have disadvantages, and some are essentially useless. Stoll (1947) has suggested that the most effective anthelmintic would be nontoxic and applicable to large population groups, such as iodides in salt, fluorides or chlorine in water, or vitamin supplements in food. The revival of interest in a chemotherapeutic approach to the design of new anthelmintic drugs promises agents that will meet Stoll's requirements.

### Screening of anthelmintic agents.

Screening of anthelmintic agents poses a special problem. The wide variations in the species of helminths, their behavior in the host, and the susceptibility of the host to the anthelmintic drug are all difficult to simulate under experimental conditions. Craig and Tate (1961) reviewed the *in vitro* and *in vivo* technics in common use. In the former, the paralysant or lethal effect of the drug is tested on isolated worms; *in vivo* efficacy is measured by a reduction of the worm infestation in animals. In these tests the chief interest has been the eradication of helminths from the intestinal tract. Undoubtedly there are many symbiotic associations between the parasite and the host, so that *in vitro* testing at best gives only a crude approximation of the effectiveness of a drug. However, *in vitro* methods permit the screening of large numbers of compounds, and "leads" for further study may be uncovered by such tests.

*In vitro* tests employ *Ascaris lumbricoides; Gigantorhynchus hirudinaceus; Uncinaria stenocephala; Trichostrongylus calcaratus;* free-living nematodes, *e.g., Anguillula aceti* or *Turbatrix aceti;* or nemathelminths such as *Heterakis gallinae* and *Rhabdias bufonis* (Craig and Tate, 1961).

*In vivo* screening may be carried out using natural roundworm, whipworm, hookworm, or tapeworm infections in dogs and threadworm infections in mice or rats. Clinical studies have shown that compounds effective in eradicating the oxyurid *Syphacia obvelata* in mice are effective as ascaricides and antioxyurids in man and farm animals (Craig and Tate, 1961). Many other experimental and natural infestations have been used, and each laboratory seems to have developed a screening technic best suited to its program of anthelmintic research.

A number of workers have studied the essential metabolic patterns of intestinal parasites in an effort to learn about biochemical differences that may exist between the mammalian host and the invading organism. These studies have been reviewed by Bueding and Swartzwelder (1957) and Craig and Tate (1961). It is possible that a true chemotherapeutic approach may be developed for the eventual synthesis of useful anthelmintic drugs.

Welch *et al.* (1947) proposed that a class of compounds related to the cyanine dyes was active as antifilarial drugs because these compounds inhibited one or more enzyme systems concerned with cellular oxidative metabolism within the helminth. Worms recovered from treated rats showed markedly depressed respiratory activity and an increased aerobic glycolysis. An extension of these observations led to the development of the drug pyrvinium pamoate, useful in enterobiasis.

The effect of cortisone and ACTH on experimental rat helminth infections has been investigated. These agents have been reported of value in alleviating the clinical symptoms of *Trichinella spiralis* infection in man. The corticosteroids are believed to modify the immune response to a nematode infection and may exert a favorable influence in clearing the infestation.

### Carbon Tetrachloride, N.F. ($CCl_4$).

Carbon tetrachloride is a heavy, volatile liquid. The drug is inexpensive and has been used extensively in the treatment of hookworm infestation. Carbon tetrachloride is a general protoplasmic poison. It has a burning taste, and when it is applied locally to the skin, it is an irritant. It is irritating to the intestinal mucosa. The drug passes through the stomach unchanged and is absorbed from the intestine. Carbon tetrachloride is hepatotoxic, and fatalities have resulted from ordinary anthelmintic doses of the drug. There seems to be no justification for the use of this substance as an anthelmintic drug. Tetrachloroethylene is superior. Andrews (1963) has reviewed the current concepts of acute carbon tetrachloride hepatotoxicity.

### Tetrachloroethylene, U.S.P. ($Cl_2C{:}CCl_2$).

Tetrachloroethylene is a clear, colorless liquid having a characteristic odor. This halogen substituted hydrocarbon is relatively nonirritating, is of low toxicity, and has been found to be very effective for the removal of hookworm. Tetrachloroethylene in adequate dosage is as effective as carbon tetrachloride against hookworm infestation and less toxic.

Tetrachloroethylene is given as a single dose of 0.06 ml./pound in a soft gelatin capsule; no more than 5 ml. is administered.

**Tetrachloroethylene Capsules, U.S.P.,** are available containing 0.5 and 1 ml. of tetrachloroethylene. Fatty foods should be avoided in the preliminary diet when this drug is to be administered. Some narcotic effects have been observed, such as dizziness and drowsiness, following the administration of tetrachloroethylene. Cases of coma lasting several hours which followed shortly after the usual anthelmintic dose of about 3 ml. of tetrachloroethylene have been reported.

Tetrachloroethylene is not absorbed to an appreciable extent from the gastrointestinal tract in the absence of fats or alcohol. In therapeutically effective doses the drug is nontoxic. Its lack of toxicity is exemplified by the fact that no serious reactions have been encountered in clinical studies on many thousands of individuals. If some absorption does occur, *vertigo, headache, nausea*, and *drowsiness* are the chief symptoms. Carr *et al.* (1954) used tetrachloroethylene in 385,000 patients with hookworms and observed that when the drug was given and not followed by a purge there was less shock to the patient and a more effective vermifuge response. The toxic effects were not serious.

Tetrachloroethylene is contraindicated in cases of ascariasis, gastrointestinal inflammation, severe anemia, alcoholism, or severe debilitation.

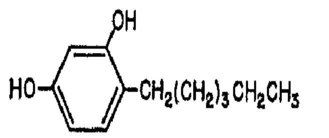
### Thymol, N.F. (Methylisopropyl phenol).

This crystalline compound occurs in the volatile oils of certain plants. Thymol has been used for hookworm eradication since 1879. It is an irritant to the mucous membranes, and when absorbed it produces stimulation and subsequent depression of the central nervous system. It possesses bactericidal properties and is commonly employed in the preservation of urine specimens. Thymol is almost completely absorbed from the gastrointestinal tract. Fat assists the absorption and must be avoided when this drug is used as an anthelmintic. It is partially destroyed in the body, and a portion is excreted in a conjugated form in the urine.

Thymol appears to have little place in therapeutics as an anthelmintic. It is a toxic drug. The advent of tetrachloroethylene therapy in ancylostomiasis and its relative lack of toxicity makes the use of thymol unnecessary.

### Hexylresorcinol, U.S.P.

Hexylresorcinol (1,3-dihydroxy-4-hexylbenzene) was introduced into therapeutics as a urinary antiseptic. It was found to be very effective against ascaris infection by Lamson in 1930. The drug is also effective against tapeworm and hookworm infestation. Hexylresorcinol occurs as white, needle-shaped crystals. It has an astringent taste and produces a sensation of numbness when placed on the tongue. It acquires a brownish pink tint on exposure to light. The drug is irritating to the skin.



Hexylresorcinol, U.S.P

The drug, when used as an anthelmintic, is partially absorbed and is excreted in the urine. Hexylresorcinol has the advantage of relatively low toxicity, and therefore anthelmintic dosage can be repeated without long intervening rest periods.

The adult dose of the drug is 1 gm. administered orally in divided doses in gelatin-coated pills.

**Hexylresorcinol Pills, U.S.P.** These pills contain 0.1 and 0.2 gm. of hexylresorcinol. The dose for children below 10 years of age is 0.1 gm. for each year of age. Care must be exercised when these pills are taken by mouth to avoid chewing the pill, as direct contact with buccal mucosa produces severe irritation. No pretreatment preparation of the patient is necessary. The drug is taken on an empty stomach in the morning, and food is omitted for 5 hours. A post-treatment daily purge is recommended. Hexylresorcinol is used in the treatment of *ascariasis*, and in mixed infections with *ascaris* and *hookworm*. The drug is less effective against pinworms, whipworms, and dwarf tapeworms.

### Santonin, N.F.

Santonin is a white, crystalline, odorless powder. It is obtained from the plant *Artemisia maritima* and related species. The compound is the inner anhydride of santonic acid. When administered as an anthelmintic, a small amount of the compound is absorbed and oxidized in the body. It is excreted in the feces and in the urine, imparting to the latter a yellow color which changes to pink when the urine is made alkaline. Occasionally in therapeutic doses it affects vision by changing color impressions to yellow (xanthopsia). In toxic doses it produces epileptiform convulsions, followed by severe depression of the central nervous system and death. As an anthelmintic in ascariasis it has been replaced by the less toxic drug piperazine.

### Aspidium Oleoresin, U.S.P.

Oleoresin of aspidium (oleoresin of male fern) is obtained as an ether extract prepared from the rhizomes and stipes of *Dryopteris filix-mas* and related species. The oleoresin should be fresh in order to meet the U.S.P. standard requirement of 24 per cent of crude *filicin*, the active anthelmintic principle.

Oleoresin of aspidium is a dark green, thick liquid, usually depositing a granular, crystalline substance which must be thoroughly mixed with the liquid portion before use. The oleoresin is insoluble in water and alcohol but soluble in ethyl ether. The official preparation contains several methane derivatives of phloroglucin. *Filicic acid*, a phloroglucin derivative, is the most important constituent.

*Oleoresin of aspidium* is used in the treatment of *intestinal tapeworm infestation*. The drug is valueless in other types of helminthiasis. It is very irritating to the gastrointestinal mucosa when administered in undiluted form. It frequently produces *nausea*, *vomiting*, *abdominal cramps*, and *dysentery* when given in the usual anthelmintic dose. Owing to its toxicity the drug has a limited value as an anthelmintic.

The adult dose is from 1 to 5 gm. Gelatin capsules of 0.5 gm. are administered at half-hour intervals on an empty stomach until the calculated dose has been given. Children under 10 years of age are given 0.5 gm. for each year, up to the adult maximum. The diet for 2 days prior to the treatment should exclude fat. A saline purgative is administered from 1 to 2 hours after the last dose of the drug. If toxic signs appear during the course of treatment, the administration of the drug should be discontinued.

After it is absorbed from the gastrointestinal tract, aspidium produces toxic manifestations involving the central nervous system. The drug should not be prescribed in the presence of ulceration of the gastrointestinal tract. Severe poisoning is manifested by *amblyopia*, *yellow vision*, *blindness*, *muscle cramps*, *tonic convulsions*, *coma*, *circulatory and respiratory depression*, and *collapse*.

The drug must be administered under careful medcial supervision.

### Methylrosaniline Chloride, U.S.P.

Methylrosaniline chloride (gentian violet medicinal) (see page 215) is a dark green, water-soluble powder. The drug has both antiseptic and anthelmintic properties. Gentian violet medicinal has been used as an anthelmintic in the treatment of *Strongyloides stercoralis* and *Oxyuris* infections.

Gentian violet has been employed successfully in the treatment of oxyuriasis, although piperazine salts are superior. The adult dosage is two 30-mg. tablets 3 times a day before meals for 10 days. For children, the dose is 10 mg. a day for each year of age; the total daily amount is divided into 3 doses. Gentian violet, because of the ease of its administration, relatively high degree of efficacy, and low cost, is of value in the treatment of these conditions.

**Methylrosaniline Chloride Tablets, U.S.P.,** are available, containing 10 or 30 mg. of the drug.

In strongyloidiasis gentian violet is administered as enteric coated tablets in a 17-day course of therapy. The dose is 60 mg., given 3 times each day.

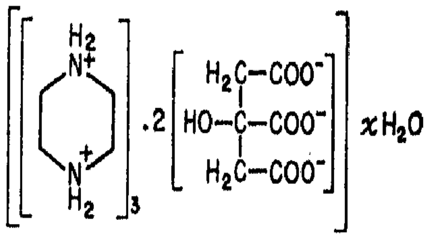
Untoward reactions following gentian violet therapy are *nausea*, *vomiting*, *diarrhea*, and *abdominal pain*. These symptoms are temporary and quickly subside when the dosage of the drug is reduced or the treatment discontinued for a day or two.

### PIPERAZINE SALTS

**Piperazine Citrate, U.S.P. (Antepar, Multifuge, Parazine, Pipizan)** is one of the most effective anthelmintic drugs to be introduced in medical practice. This substance does not have an objectionable taste, it is relatively nontoxic, and is the anthelmintic of choice in pinworm and roundworm infestations.

Piperazine is not a new drug. It was first employed 60 years ago in large doses in the treatment of gout and urinary lithiasis. A substituted piperazine, Diethylcarbamazine Citrate, U.S.P., (see page 166) has had rather extensive use in filariasis. Brown and associates (1954) and Swartzwelder *et al.* (1955) used piperazine citrate in ascariasis.

Piperazine citrate is prepared by the reaction of an excess of piperazine hexahydrate with citric acid. The resulting salt occurs as a white, crystalline powder. Its structure may be represented as follows:



Piperazine Citrate, U.S.P.

**Piperazine tartrate (Piperat), piperazine adipate (Entacyl), piperazine phosphate and gluconate** are also used as dosage forms of the drug.

**Piperazine calcium edathamil (Perin)** is a chelated compound produced by reacting piperazine with edathamil and calcium carbonate. In solution, all these salts of piperazine form the hexahydrate, and dosage is based on the formation of this compound.

**Piperazine Citrate Syrup, U.S.P.,** is a flavored syrup of piperazine citrate containing an equivalent of 100 mg. of piperazine hexahydrate per ml. The oral dose for children and adults is calculated on the basis of 50 mg./kg. The total daily dose is usually limited to 2 gm. The best results have been obtained by dividing the daily dose into 2 equal parts, administered morning and evening. Swartzwelder *et al.* (1955) found a *single* dose of 70 mg./pound was almost always effective in eliminating light, moderate, and heavy infestations with *Ascaris lumbricoides*. Most workers have used a dose schedule of 5 to 7 days. Brown (1960) has reported that therapy on 2 consecutive days will cure approximately 95 per cent of infected persons.

In pinworm infections the course of treatment is usually 2 weeks. Some clinicians have used an alternate weekly schedule with a rest period of 1 week between the 7-day dosage periods.

Toxic reactions to piperazine citrate therapy have been minimal. Piperazine hydrate has been reported to have produced giddiness, lack of coordination, difficulty in focusing vision, and a sense of detachment. These effects are believed to be the result of excessive dosage. The effects disappeared when the drug was discontinued. Chronic toxicity studies with piperazine citrate have failed to reveal a significant effect on the blood elements (Brown, 1954). Side effects of a less serious nature have been reported. These are infrequent and consist of nausea, vomiting, headache, abdominal cramps, and, very rarely, urticaria. The low toxicity of piperazine citrate makes it one of the most promising anthelmintic drugs. The preparation is highly acceptable to children, easily administered, and requires no fasting period.

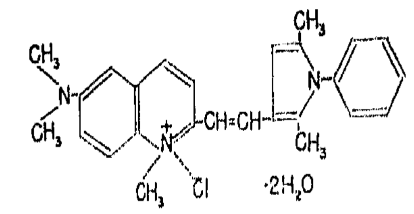
### THE CYANINE DYES

Early studies designed to demonstrate anthelmintic activity evaluated compounds *in vitro* against the filarial worm of the wild cotton rat, *Litomosoides carinii*. The cyanine dyes were found to be extremely effective in inhibiting oxygen uptake and increasing aerobic glycolysis of this parasite. Further, concentrations of the dyes 1000 times higher than those exhibiting an inhibitory effect on respiration of the worms had no effect on oxygen uptake of mammalian tissue slices or homogenates. Therefore, these compounds interfere with the respiratory enzyme systems of the worms without exhibiting a similar enzymic effect on animal tissues. The chemotherapeutic index is high, for the compounds are not appreciably absorbed from the gastrointestinal tract of man.

As a group, the cyanine dyes contain the *amidinium* ion. This ion is characterized by a quaternary nitrogen separated from a tertiary nitrogen by a "resonating or conjugated carbon chain of alternating double and single bonds." A number of amidinium compounds exert antifilarial activity, and effectiveness is not restricted to any particular ring. However, any modification which eliminates the amidinium ion resonance destroys the metabolic and chemotherapeutic activity against the experimental worm *Litomosoides* (Bueding and Swartzwelder, 1957).

As a result of extensive studies of this class of compounds, two anthelmintics useful in man have been developed, pyrvinium pamoate and dithiazanine iodide.

**Pyrvinium pamoate (Porvan).** Pyrvinium chloride was synthesized by van Lare and Brooker (1950) in the chemotherapy program for filariasis during World War II. Subsequently it was discovered to have anthelmintic properties. Weston *et al.* (1953) found the substance to be much more effective than gentian violet in experimental and natural pinworm infections in mice. These observations and the drug's low toxicity led to its trial in human oxyuriasis, with encouraging results.



Pyrvinium Chloride

Pyrvinium pamoate was found to be a superior pharmaceutical form of the drug. It has proved to be highly curative and well tolerated when administered as a single oral dose of 5 mg./kg.

Pyrvinium pamoate is the bis-6-dimethylamino-2-[2-(2,5-dimethyl-1-phenyl-3-pyrrolyl)vinyl]-1-methylquinolinium salt of 4,4′-methylenebis-(3-hydroxy-2-naphthoic acid). It is a deep red, crystalline solid which is stable to heat, light, and air. It is highly insoluble in water, which may account for its superior intestinal anthelmintic properties as compared with the chloride salt.

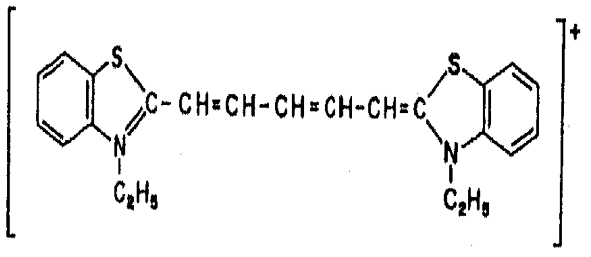
Beck and associates (1959) demonstrated that a single dose of pyrvinium pamoate, 5 mg./kg. expressed as the base, would successfully eliminate pinworm infections. Comparative studies by other workers have shown a cure rate of 96 to 100 per cent of infected persons within a 2-week period following treatment. The availability of such a single dose regimen may indicate that pinworm infestation may be effectively controlled in the future. Certainly the problems of cross-infection and reinfection in members of a family can be adequately overcome by the use of this drug.

A flavored suspension of pyrvinium pamoate is available for oral use in which each ml. contains the equivalent of 10 mg. of the pyrvinium base. Coated tablets contain the equivalent of 50 mg. of the pyrvinium base. The dose is a 5-ml. teaspoonful of the suspension or 1 tablet/10 kg.

Serious toxic effects have not been reported following the use of pyrvinium pamoate. The incidence of nausea and vomiting has been low. Patients should be informed that the drug will color the stools a bright red.

**Dithiazanine Iodide, U.S.P. (Abminthic, Delvex).** The discovery of the therapeutic activity of dithiazanine was made by McCowen and his colleagues (1957). This compound proved to be a safe and effective agent for oral therapy of trichuriasis. Dithiazanine iodide is 3,3′-diethylthiadicarbocyanine iodide.

Dithiazanine iodide is a blue cyanine dye, only slightly soluble in water. The drug is very effective against whipworms and *Strongyloides stercoralis.* Unlike results with many anthelmintics, cure rates as high as 75 to 100 per cent have been reported for trichuriasis and strongyloidiasis. Not all reports have indicated such satisfactory results, but undoubtedly dithiazanine is far more effective than earlier forms of treatment of these helminth infections. The evidence indicates that this drug effects a cure of infestation rather than simple elimination of the major portion of the infecting worms.



Dithiazanine Iodide

Dithiazanine is also an effective anthelmintic against hookworm, but best results are obtained by combined therapy with tetrachloroethylene. Most investigators have found dithiazanine as effective as piperazine in pinworm infections, but the latter drug is preferred because it is less likely to cause gastrointestinal side effects and is potentially less toxic. Swartzwelder *et al.* (1958) found dithiazanine effective in mixed infections of trichuriasis and ascariasis. Some parasitologists prefer to reserve dithiazanine therapy for mixed pinworm and roundworm infections in those patients in whom a course of piperazine treatment has been ineffective.

Dithiazanine iodide is administered orally. The drug has been given in the form of tablets or a cherry-flavored suspension containing 20 mg./ml. The daily dose is 45 mg./kg. or 20 mg./lb., divided into 3 portions. A course of treatment should last for 5 to 10 days in trichuriasis, and 7 to 21 days in strongyloidiasis. A maximum daily dose of 600 mg. should not be exceeded.

Extensive laboratory studies conducted on patients receiving 600 mg. of dithiazanine daily for 3 weeks have not shown significant deviations from normal values. The urine excreted by these subjects was not colored, and sensitive chemical tests did not detect the compound, indicating that the drug is not excreted in the urine. It is apparently not absorbed from the gastrointestinal tract. The stools are colored blue by the drug. Nausea, vomiting, and anorexia are side effects produced by dithiazanine and are likely to be related to its local irritant effect on the gastrointestinal mucosa. Abdominal cramps and diarrhea have been experienced by patients taking the drug. It is discontinued if there is a bluish-green color in the urine. Deaths have followed the use of the drug. Dithiazanine should be prescribed with caution in patients with renal disease because related compounds have been found to be nephrotoxic (Stemmermann and Nakasone, 1960).

**Quinacrine as an anthelmintic.**

Atabrine or quinacrine (see page 149) was discovered to combine in an extraordinary way with the tissue cells of the head of the tapeworm *T. saginata* (Keller, 1949). *In vitro* the head of the worm is stained and appears as a strongly fluorescing body after contact with a solution of the antimalarial drug. Tissue sections from expelled worms after quinacrine therapy revealed that the drug was only concentrated in the head of the worm. Keller postulated that quinacrine behaves as an electropositive dye and combines with the electronegative cells of the head of the worm, causing a reversal of electrochemical forces and a resulting relaxation of the holding muscles. With a loss of function of the head or "hold-fast organ," the worm was expelled by natural peristaltic action. The drug is not toxic to the worm and thus elicits a true vermifuge effect.

Quinacrine has been used with success in *T. saginata, T. solium, Diphyllobothrium latum,* and *Hymenolepis nana* infestations. A dose of 0.2 gm. every 10 minutes for 4 doses followed by a saline laxative after 2 hours was the course of treatment. To allay nausea, 0.6 gm. of sodium bicarbonate may be given with each dose of quinacrine. Some workers prefer to administer 10 mg. of prochlorperazine before treatment and about 4 hours after.

The preparation of the patient is important: a liquid diet is administered the day before treatment, and food is omitted in the morning before drug administration is begun. Because contact between the worm and the drug is necessary, the intestine should be free of food.

With suitable preparation of the patient, proper drug dosage, and identification of the head of the worm, a cure rate of 70 per cent for *T. solium* has been claimed. Some authors have reported that a repetition of quinacrine on the second day will remove recalcitrant cestodes. Treatment must be repeated after several weeks when *H. nana* is present because all the worms are not in the same stage of development at one time. Unfortunately, the degree of success in clearing *H. nana* infestations is low.

Quinacrine is the most effective and least toxic drug for the treatment of cestodiasis. The side effects associated with its use are discussed in Chapter 12. Recently, the related antimalarial drugs chloroquine (Aralen) and amodiaquine (Camoquin) have been reported to be effective in treating *Taenia* infestations. The discovery of the usefulness of these relatively nontoxic drugs as anthelmintics is particularly noteworthy. Quinacrine is the safest and most effective therapeutic agent available in the treatment of tapeworm infection (Brown, 1960).

### Recently Introduced Anthelmintics

**Bephenium hydroxynaphthoate (Alcopar).**

In the course of routine screening of a new series of quaternary ammonium compounds, Copp *et al.* (1958) observed that certain members of the group possessed activity against parasitic nematodes. N-benzyl-N,N-dimethyl-N-2-phenoxyethyl-ammonium hydroxynaphthoate, known as bephenium hydroxynaphthoate or Alcopar, proved to be effective against human hookworm, *Necator americanus* and *Ancylostoma duodenale*. Other salts of this compound are used in veterinary practice as anthelmintics.

A single dose of 5 gm. of Alcopar granules, which is equivalent to 2.5 gm. of bephenium base, is the recommended dose. Repeated administration over a 5-day period is more effective. Young and associates (1958) found that the drug eliminated about half the worms in 14 patients after a single dose of 1.2 gm. of the chloride salt (1.05 gm. of the base), while 6 gm. (5.28 gm. of the base), given over 5 days to 6 patients, was more effective. The drug has also been employed in trichuriasis and in ascariasis. It is only moderately effective against *T. trichiura*. The side effects consist principally of nausea, vomiting, and abdominal pain. As more experience is gained with this drug, its place as an anthelmintic will be determined.

**Yomesan.**

Yomesan (N-[2′-chlor-4′-nitrophenyl]-5-chlorsalicylamide) has been reported to be effective against *H. nana* infestations and other types of tapeworms. The drug seems to be well tolerated (Lloyd, 1961; Donckaster *et al.*, 1961).

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# Part III

## THE RESPONSE OF THE SKIN AND MUCOUS MEMBRANES TO DRUGS

## 15

## *The Pharmacologic Response of the Skin and Mucous Membranes*

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Many kinds of drugs are employed in medical practice for their action upon the skin and mucous membranes. Most of these substances are used for their local pharmacologic effects. In this section we shall consider the protective drugs, the counterirritants, the local anti-infective drugs, the local anesthetics, and those drugs used for their effect upon the gastrointestinal tract.

### The Functions of the Skin

The quality of the skin of man is a diagnostic criterion of his state of health. In disease the skin may reflect in many ways the severity and kind of illness. Because the subject of dermatologic therapy is so vast, only the pharmacologic principles can be outlined here. However, there is an aspect of drug therapy in general that relates to the skin. When administered systemically, many drugs cause the skin to respond as a shock organ. Thus one of the most common side effects produced is skin eruption, erythema, or "dermatitis medicamentosa." Consequently, the physician often finds that it is necessary to treat skin lesions that have resulted from the use of the drug that be prescribed. On the other hand, there are many contact allergies—poison ivy dermatitis, for example—that may be assuaged by the use of a local application. Certain of these' conditions which are amenable to drug therapy are considered in this chapter.

Throughout the text many references are made to the dermatologic aspects of drug therapy. Systemic medication with antibiotics and antifungal and antihistaminic agents are examples of drugs used in dermatology. The topical application of these drugs and their combined therapy with the corticosteroids are considered in the sections specifically dealing with these agents.

In the evaluation of therapeutic agents applied locally to the skin, it is possible to use the method of simultaneous symmetrical paired comparison (Sulzberger *et al.*, 1946, 1962). In such a test similar skin lesions situated on symmetrical sites in the same individual are treated, one with a therapeutic agent and the other with a suitable control preparation. Modern pharmacotherapy in dermatologic practices has been established by the use of such technics.

The skin is an important regulatory organ. In an adult it weighs approximately 4 kg. and is estimated to contain from 2 to 5 million sweat glands. The most significant functions of the skin are *protection*, *heat regulation*, *prevention of bacterial invasion*, *ergosterol activation*, *excretion of body water and electrolytes*, and *sensory detection*.

### Protection.

As a mechanical barrier the skin is elastic and tough and will tolerate a considerable degree of injury before being penetrated. Unbroken skin is almost completely impervious to water; when dry it is a poor conductor of electricity and is chemically inert. It is a poor heat conductor and hence possesses thermal-insulating properties. The melanin pigment protects the underlying tissues from mild ultraviolet radiation exposure.

### Heat regulation.

In addition to its insulating properties the skin possesses the capacity to regulate the body temperature under the control of the nervous system. In a high environmental temperature, the superficial vessels dilate, with a consequent loss of heat by conduction and radiation. The eccrine sweat glands are stimulated to activity. Increased sweating and the evaporation of fluid result in a lowering of the temperature of the body surface.

### Prevention of bacterial invasion.

The most casual observer is impressed with the value of the skin as a barrier against infection. The subcutaneous structures are more susceptible to bacterial invasion. In addition to serving as a simple barrier to infection, there appears to be some complex biologic mechanism which enables the skin to free itself from most of the microorganisms that are continuously impinging upon it; however, there are normal resident bacterial flora.

The self-sterilizing action of skin can be studied by measuring the rate of disappearance of hemolytic streptococci from a measured culture applied to the skin. Normal skin possesses a limited capacity to destroy these organisms. Fleming (1922) observed a thermolabile substance in tears, sweat, and skin capable of lysing bacterial cells. This substance has been designated lysozyme. Numerous enzymes have been identified in the apocrine and eccrine glands, the dermis and epidermis, and the hair follicles. The presence of active enzyme systems in these structures has led to histologic technics that are useful in defining the structure and functions of these cellular units of the skin (Montagna, 1962).

Bacterial protection is afforded the skin by its normally acid reaction (pH 4.5 to 6.0). This "acid mantle" is said to have anti-bacterial properties. The glandular orifice is a particularly vulnerable point for bacterial invasion, and many bacterial skin lesions originate in the skin glands.

There are normal resident bacterial flora on the skin. These flora consist principally of micrococci, diphtheroids, (corynebacteria), *Candida albicans*, and propionibacteria. Presumably these organisms do not cause disease as long as they remain on the surface of the skin. Even after penetration to the deeper structures, these resident microorganisms are not considered pathogenic (Blank, 1959).

### Ergosterol activation.

Certain natural sterols present in the lipids of the skin serve a useful metabolic function; for example, in the skin ergosterol is activated by exposure to ultraviolet light or sunlight to form vitamin D.

### Excretion of water and electrolytes.

Normally in an adult the skin excretes approximately 500 ml. of water every 24 hours. Under the influence of some drugs this quantity of fluid may be greatly increased. Drugs that increase the secretion of sweat are called *sudorifics* or *diaphoretics*. The electrolytes of human sweat are largely sodium, potassium, and chloride ions. Nitrogen may be lost from the body in the sweat as urea. Normal sweat contains approximately 0.3 per cent NaCl and 0.2 per cent urea.

Shelley and Hurley (1953) postulated that apocrine sweating is under the control of adrenergic fibers. In well-controlled studies on men and women, apocrine sweating was produced by the injection of epinephrine or norepinephrine or evoked pain and fear. Heat and emotional stress produced eccrine (exocrine) sweating. They suggest that the apocrine gland cells form sweat by true secretion. This sweat may then be stored in the gland until adrenergic stimuli cause its expulsion. This they differentiate from the true osmotic cellular process of secretion of sweat. This latter process is likely under parasympathetic influence (Montagna, 1962).

### Sensation.

The action of drugs on the sensory nerve endings, the local anesthetics, are considered in a subsequent chapter.

### Effect of Chemical Agents on Skin Pigmentation

There are numerous dermatologic aspects of skin pigmentation and achromasia that are of pharmacologic significance. Skin pigment changes that occur as side effects are discussed in a consideration of the drugs that elicit these effects. Some agents applied topically to the skin serve as "sun screens" and have a minor therapeutic significance. Following systemic administration, other drugs and chemicals have been discovered to produce skin changes that may prevent light-sensitive eruptions in susceptible subjects. Both chloroquine (Aralen) and quinacrine (Atabrine) (see page 149) have been used experimentally for this purpose (Lamb, 1959). Recently, a systemically administered agent, methoxsalen, has been discovered that encourages tanning of the skin. It has been used for cosmetic purposes and to relieve the marked achromatic areas of the skin in vitiligo (Stegmaier, 1959).

**Methoxsalen (Meloxine, Oxsoralen).** The plant *Ammi Majus Linn* was used in ancient Egyptian folk medicine to restore pigmentation in vitiliginous skin areas. From extracts of this plant active pigment-stimulating ingredients have been isolated as a group of furocoumarins. Psoralen is a furocoumarin and methoxsalen is 8-methoxypsoralen, or 8-MOP.

Oral ingestion of methoxsalen and repeated exposure to natural or artificial ultraviolet irradiation can induce pigmentation in some depigmented skin areas in vitiligo and tanning in normal skin. However, according to Sulzberger and Lerner (1958), the clinical response is erratic and unpredictable, and cosmetically satisfactory repigmentation can be obtained in only about 1 out of 7 patients treated. As the systemic side effects and chronic toxicity have not been completely studied, the cosmetic use of this agent to produce an accelerated sun tanning of the natural skin is unwarranted.

**Monobenzone, N.F. (Benoquin)** is *p*-benzyloxyphenol. This ether of hydroquinone is a melanin pigment inhibitor. The chemical inhibits tyrosinase and thus blocks the oxidation of tyrosine to dihydroxyphenylalanine. Phenylalanine is a precursor of melanin pigment in the skin. The effects are temporary. The chemical is applied topically as a 20 per cent ointment or 5 per cent lotion 2 to 3 times daily until the desired degree of skin depigmentation has been obtained. Dermal irritation and mild to severe erythema and dermatitis may follow the use of this agent. Systemic toxicity resulting from external use of the substance has not been observed.

### Classification of Drugs Applied to the Skin and Mucous Membranes

### Emollients.

Emollients, or skin softeners, are usually fatty substances applied to the surface of the skin to protect or soften it. Bland ointments serve as protective substances. Active medicinal ingredients may be incorporated into these ointments.

Hinkel *et al.* (1953) made quantitative studies of the amount of an emollient deposited on the skin under experimental conditions. From ultraviolet and infrared absorption data they were able to measure the influence of synthetic surface-active agents upon emollient fat adsorption on the skin surface. They found that very small quantities of "superfatted synthetic detergent" formulations are capable of producing an emollient effect. For example, only 3.3 mg. of the surface-active agent Triton 200 is deposited on the skin of the hand with a surface area of 400 sq. cm. By calculation this amount can be shown to be sufficient to form a monomolecular layer on the skin. It appears that the strongly anionic detergent is attached to the cationic groups of the protein of the skin. The oriented sulfonic and ether groups are anchored to the protein of the skin with the lipophilic portion of the molecule exposed on the surface area. The skin surface is thus altered and made more lipophilic. Fat constituents of the emollient preparation will dissolve in the lipophilic hydrocarbon tails of the detergent molecule, forming 1 or more protective layers. The most effective emollient action is achieved by combining a surface-active detergent with a suitable fat base. Most modern emollient preparations combine these two ingredients.

**Petrolatum, N.F.,** is an ointment base frequently employed. **Wool Fat, U.S.P. (anhydrous lanolin)** is a purified fat of sheep's wool, a light yellowish, tenacious, unctuous mass with a slight, somewhat unpleasant odor. It is composed chiefly of *cholesterin.* Wool fat is miscible with its own weight of water without losing its ointment consistency. Its capacity to absorb aqueous fluids makes it useful when prescribing water-soluble drugs in ointment form. **Hydrous Wool Fat, U.S.P.,** contains from 25 to 30 per cent water. The Pharmacopeia recognizes **Hydrophilic Ointment, White Ointment, Hydrophilic Petrolatum,** and **Petrolatum Rose Water Ointment** as suitable ointment bases.

Chemistry has produced a large number of synthetic chemicals possessing unusual physical properties that permit mixing water- or oil-soluble drugs in either hydrophilic or hydrophobic emollient ointment bases. Oleaginous ointment bases consisting of hydrophobic greases will not take up aqueous solutions. Petrolatum and *Plastibase,* a new type of ointment base containing 95 per cent liquid petrolatum and 5 per cent polyethylene, are hydrophobic bases.

Hydrophilic oleaginous substances such as **Hydrophilic Ointment, U.S.P., Plastibase hydrophilic, Polysorb anhydrous,** and **Aquaphor** are absorbent ointment bases which will take up water or aqueous solutions of drugs.

Water-miscible ointment bases, in which oil is dispersed in an aqueous external phase of a semisolid emulsion, are essentially vanishing creams. These relatively greaseless ointments wash off the skin easily; cosmetically, they are more attractive than greases. Many commercial creams are available for example, *Neobase* and *Unibase.*

Water-soluble demulcent and emollient ointment bases are made from synthetic polyethylene and polyol condensation products. These are suitable for dermatologic use as vehicles for many water-soluble or oil-soluble drugs.

**Castor Oil, U.S.P.,** applied externally, is a bland emollient to the skin. The oil is instilled in the eyes before anesthesia with the volatile aliphatic ethers to protect the corneas from the irritation of the vapors of these agents.

### Collodion.

Collodion, U.S.P., is a solution of nitrated cellulose in a mixture of alcohol and ether. When placed on the skin the ether and alcohol evaporate, leaving a protective pellicle similar in appearance to the skin. The film is waterproof and may be used to cover small aseptic and dry skin defects.

### Dusting powders.

Dusting powders are inert materials used in the treatment of skin abrasions. Medicinal dusting powders containing an active antiseptic ingredient may be prepared by incorporating the drug in the dry powder form into the dusting powder base. **Kaolin, N.F.,** a native aluminum silicate, and **Talc, U.S.P.,** a native magnesium silicate, are frequently employed as dusting powders. These substances desiccate the area of application, dry secretions, and provide an unfavorable environment for bacterial growth. Kaolin is a soft, white powder. Because of its capacity to absorb toxins and its soothing protective action, kaolin is used in the treatment of irritations of the mucous membranes of the gastrointestinal tract.

**Zinc Stearate, U.S.P.,** is a water-shedding powder and has the advantage of clinging better to skin surfaces, thus affording protection from watery discharges.

### Keratolytics.

Keratolytic drugs are used for the removal of excess horny layers of the skin, such as corns and callosities. Keratolytic ointments and lotions are generally employed. **Benzoic and Salicylic Acid Ointment, U.S.P.** (Whitfield's Ointment) is a keratolytic ointment. This ointment contains 6 per cent benzoic acid and 3 per cent salicylic acid in a water-soluble polyethylene glycol ointment base. **Compound Resorcinol Ointment, N.F.,** exhibits a mild keratolytic effect.

**Selenium Sulfide Detergent Suspension, U.S.P. (Selsun Sulfide)** is a mixture of crystalline selenium monosulfide and solid solutions of selenium and sulfur in an amorphous form. It is employed externally as a 2.5 per cent suspension for application to the scalp in the treatment of *seborrheic dermatitis* and dandruff. It may be useful in *psoriasiform seborrhea, seborrhea oleosa, acne vulgaris,* and *atopic eczema.* It is not effective in scalp ringworm caused by *Microsporum audouini.*

The preparation should not be used in the presence of skin inflammation or exudative skin lesions. Systemic absorption is to be avoided, and patients should be instructed to wash their hands and clean beneath their fingernails to remove traces of the drug after each topical application. Selenium sulfide is highly toxic if ingested, and care must be exercised to avoid accidental oral consumption. While sensitivity reactions have rarely been reported, hypersensitivity to selenium may be encountered.

The symptoms of selenium intoxication that have been reported following the use of selenium sulfide shampoo 2 to 3 times weekly for 8 months were arm and hand tremors, severe sweating, metallic taste, and generalized tremors. Malaise with dull, continuous pain in the lower abdomen, weakness, and lethargy were described in one case by Ransone (1961).

**Cadmium sulfide (Capsebon)** is used in the form of a 1 per cent suspension applied as a therapeutic shampoo in the treatment of seborrheic dermatitis (seborrhea capitis). It is as effective as selenium sulfide in controlling the symptoms of seborrhea. These agents are not considered curative. Cadmium sulfide is essentially nontoxic when used in the manner prescribed. Contact dermatitis may occasionally develop. The compound CdS does not appear to be absorbed appreciably from the intact skin, and systemic toxicity has not been reported following topical use.

An interesting concept has been proposed, based upon physiochemical models, that the sulfur atom of the heavy metal sulfides is the therapeutic element, while the metal serves as an activator. Thus selenium may act as an intramolecular catalyst, making the tissue sulfur more active. The activation of sulfhydryl groups in epidermal tissue may alter the metabolism of the cells.

**Tellurium dioxide suspension (Teles Suspension)** is a 2.5 per cent tellurium dioxide suspension shampoo used in the treatment of seborrhea capitis. According to Gross and Wright (1958) and others, this preparation afforded satisfactory results in most patients as a means of controlling this condition. Laboratory studies have not demonstrated toxicity in animals following application of a 2.5 per cent suspension. Human subjects using the suspension as a shampoo have not experienced local irritation or oiliness of the scalp.

### Astringents.

Astringent substances are capable of causing limited coagulation of proteins, resulting in a shrinkage of the volume of cells. Their gross effect, when applied to the skin or mucous membranes, is one of shrinkage. The astringent action of tannins on the mucous membranes of the mouth is commonly recognized. **Tannic Acid, N.F.,** in solution and **Tannic Acid Glycerite, N.F.,** exhibit astringent and local hemostatic properties. In collyria, **Zinc Sulfate, U.S.P.,** in concentrations of 0.1 to 1 per cent is employed as an astringent (see page 248). **Zinc Chloride, N.F.,** is more strongly antiseptic and astringent.

### Demulcents.

Demulcents are softening agents, usually protective colloids. Therapeutically, the demulcents are used to provide protection for mucous membranes. Mucilaginous substances capable of allaying irritation will provide relief in stomatitis and gingivitis. **Acacia** or **gum arabic** and **tragacanth** or **gum tragacanth** are demulcent gums. A 6 per cent mucilage of tragacanth and a 35 per cent mucilage of acacia are official. These preparations are suitable as vehicles for the suspending of insoluble drugs and as demulcent bases for the application of medicinal agents to mucous membranes. Other demulcent substances are **karaya gum (Sterculia Gum, N.F.), quince seed mucilage,** and **Methylcellulose, U.S.P.**

The corrosive action of poisons may be allayed by the application of demulcents to the skin or mucous membranes. The most readily available demulcent substance is raw egg white.

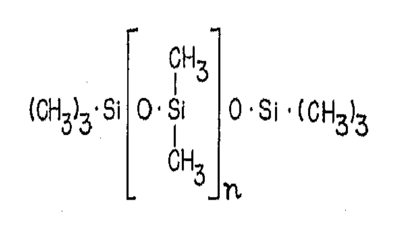
**Synthetic gelatinous demulcent bases.** In recent years new substances have been synthesized which possess surface activity suitable for use as demulcent bases. New words have been coined to describe these materials. Because they occupy an increasingly important role in modern drug therapy from the standpoint of dosage forms, a description of these substances is presented here.

The oleic, palmitic, and stearic acid esters of the ethylene oxide condensation products of sorbitan are known as *Tweens.* The *Spans* are partial esters of fatty acids and hexitol anhydrides derived from sorbitol. The *Myrj* products are made by direct reaction of the fatty acid with an alkylene oxide. These substances are dispersing agents in which oils may be solubilized to a limited degree. Some are lipophilic and some are hydrophilic. Certain members of the class are gelatinous demulcent bases and may be used as vehicles for the application of drugs to the skin. The *Carbowaxes* are mixtures of certain polyethyleneglycols. They are water-soluble and vary in consistency from unctuous materials to hard waxes. These substances do not produce irritation to the skin or mucous membranes when applied in a diluted form.

The Pharmacopeia recognizes **Polyethylene Glycol 400, Polyethylene Glycol 4000** (Carbowax 4000), and **Polyethylene Glycol Ointment.** The ointment is a typical water-soluble ointment base. Tween 80, which is the oleic acid partial ester of the ethylene oxide condensation product of sorbitan, is official under the name of Polysorbate 80. It is also called *Polyoxyethylene (20) sorbitan mono-oleate,* and *Sorethytan (20) mono-oleate.* **Polyoxyl 40 Stearate, U.S.P.** (Myrj 52) is **Polyoxyethylene 40 mono-stearate** and is used in hydrophilic ointment.

The National Formulary recognizes **Polyethylene Glycol 300,** and **Polyethylene Glycol 1540** as ointment bases.

**The silicones as skin protectives.** The silicones are polymers of organic polysiloxane ethers. They may be represented by the following formula:



$$(CH_3)_3\cdot Si\left[O\cdot \overset{CH_3}{\underset{CH_3}{Si}}\right]_n O\cdot Si\cdot(CH_3)_3$$

Silicone Polymer

The silicones as a class range from oily fluids to viscous, semi-solid masses like petrolatum. They are water-repellent and impart a permanent nonwetting film on surfaces. The silicones may be employed to form a nonwetting film on the inside of medicine vials, hypodermic syringes, and blood containers. When applied to the skin they form a "chemical glove" or cloak that serves as a protective film.

*Dimethicone* (*Covicone, Silicote*). This preparation is 30 per cent dimethyl polysiloxane with nitrocellulose and castor oil in a vanishing cream base. When applied to the skin dimethicone imparts a coating effect that is resistant to removal by soap and water for variable periods of time. Organic solvents may dissolve the film, although the process of removal is not a simple matter of solubility. The application of a hand cream containing the silicones in a suitable base twice a day for 2 weeks is said to build up a protective film that is difficult to remove. These preparations have been tried in dermal irritations caused by direct contact irritants. They are of little value when used in chronic dermatoses to avoid physical contact with the offending agent.

The silicone preparations may be irritating to the normal skin of infants. They should be applied with care to open lesions of the skin. Generally, however, these protective creams and lotions are benign.

## REACTIONS OF THE SKIN TO CHEMICAL IRRITANTS

### Local irritation produced by drug injections.

Methods have been developed to assess the degree of irritation produced by the subcutaneous injection of drug solutions. In 1937 Tainter and his associates described a technic using intravenously administered trypan blue, which seeks out and stains the site of injury caused by the injection of an irritant beneath the skin layers. Hoppe *et al.* (1950 *et seq.*) adapted this test to the routine determination of the irritancy of a number of drugs. The intensity of staining at the injection site in rabbits is graded and is related to the concentration of the drug solution and its inherent irritating character. A skin-twitch test in the dog also has been developed to measure local tissue response to hypo- and hypertonicity and pH changes in normal saline and drug solutions (Hoppe *et al.*, 1959). Sting or pain associated with intradermal injection in human subjects appears to be intimately associated with irritancy as measured by these methods. Ideally, parenteral drug solutions would be devoid of irritating properties and hence would not produce sting or pain upon injection.

The studies of Zweifach and his associates (1959) have shown that the skin circulation is influenced by hormones, including serotonin, epinephrine, norepinephrine, and histamine. Tissue damage is associated with the local release of these substances, probably from mast cells which accompany the small blood vessels prominent in ectodermal structures. Histamine liberators like 48/80 (alkophenyl-alkylamine formaldehyde condensation product) also release pharmacologically active substances including serotonin, various esterases, and heparin. Animals that have been pretreated by administration of 48/80 to deplete the available stores of vasoactive intermediaries do not experience petechial or capillary damage in the skin after trauma in the rotating Noble-Collip drum. This suggests that tissue reaction to traumatic injury is related to the liberation of these vasoactive substances locally. Adrenergic blocking agents, *e.g.*, dibenzyline, and antihistaminic agents will antagonize the experimental skin lesions produced by the endotoxins of gram-negative bacteria and epinephrine in the skin of rabbits. It appears that undue emphasis has been placed on histamine alone in a consideration of urticarial reactions and skin injury from trauma, burns, or chemical agents. Consideration is given to this matter in the chapter on allergic diseases.

### Local effects produced by irritation of the skin.

The application of irritating substances to the skin is followed by a series of changes that have been classified as *erythema, vesiculation, pustulation,* and *corrosion.* These stages represent increasing degrees of irritation. The intensity of response of the skin depends upon not only the nature of the irritant employed, but also its concentration, the solvent in which it is dissolved, and the period of contact.

Erythema, or a red coloration of the skin, is the result of vasodilatation. A drug that produces only this degree of irritation is spoken of as a *rubefacient.* Vesication is the result of prolonged, wide dilation of the skin capillaries. The vessels become more permeable, plasma escapes to the extracellular spaces, and fluid collects under the epidermis. Vesicles on the skin are characteristic of this degree of irritation. Substances that produce this type of skin irritation are called *vesicants, e.g.,* the vesicant war gases. Pustulation may result from vesicle formation and is characterized by skin pustule formation. Permanent scarring may be produced by the action of irritant drugs that elicit pustulation or corrosion of the skin.

The therapeutic use of irritants applied to the skin will be discussed in the section on *counter-irritants.* Because of the prevalent nature of *Rhus* hypersensitivity, the perplexing form of dermatitis resulting from contact with these plants will be considered here as a kind of chemical irritant.

**Rhus dermatitis.** The sensitization reaction that results from contact with poison ivy (*Rhus toxicodendron radicans*), poison oak (*R. toxicodendron diversilobum*), or poison sumac (*R. toxicodendron vernix*) is classified as *Rhus* dermatitis. The sap or plant juice produces a typical hypersensitivity reaction, which is repeated upon reexposure. Erythema and itching may develop in a few hours or a few days, but more often symptoms begin 24 to 48 hours after contact with the oily sap. The degree of reaction of a given individual may vary and may change during his lifetime. In general, children are more sensitive than adults. A consideration of those drugs useful in *Rhus* dermatitis is given here because these agents are not anti-bacterial but serve largely as skin protectives.

There is extensive literature dealing with the chemistry of dermatitis-inciting agents of the *Rhus* family of plants and the large number of proposed remedial agents. Dawson (1956) reviewed the chemistry of poison ivy extractives. It has been shown that there is a relationship between the structure and activity of the alkyl and alkenyl catechols of the poison ivy principle. When brought in contact with the skin, active compounds form a complex with specific proteins. The view is proposed that this protein-phenol complex initiates the events leading to the typical clinical symptoms of *Rhus* dermatitis. The formation of this complex apparently occurs to a maximal extent when the phenolic hydroxyl groups are in suitable positions and when there is a side chain of the proper length on the phenolic nucleus. It is also suggested that the geometrical configuration of the olefinic bonds in the side chain may be of importance in the formation of the protein complex. Therapeutic agents may prevent *Rhus* dermatitis by chemically reacting with specific structural groups and thus inactivate the inciting compounds.

Treatment of *Rhus* dermatitis involves the prompt removal of the irritating plant juice or sap. After the protein complex reaction has taken place, *the lesions will appear,* therefore the therapy is symptomatic. Antihistaminic drugs have been found to be of value in reducing the severity of the dermatitis, but they are not prophylactically specific.

**Zirconium oxide,** also called zirconium dioxide, is a heavy white powder, insoluble in water. According to Caspers (1957) and others, zirconium oxide renders the active principles in *Rhus* plants inactive. A 4 per cent lotion of zirconium oxide has been used in the treatment of poison ivy dermatitis with satisfactory results. There was no evidence of systemic toxicity. Zirconium oxide did not produce symptoms of chronic or acute toxicity upon oral administration to experimental animals. The substance did not produce skin sensitization on topical application. Clinical trials suggest that preparations of zirconium oxide are useful prophylactically in preventing *Rhus* dermatitis. Numerous preparations are available containing zirconium oxide and antihistaminic agents for use in the treatment of *Rhus* dermatitis. They appear to be of little value for this condition after skin lesions develop.

## COUNTERIRRITANTS

Counterirritants are agents used to irritate the intact skin for the purpose of relieving pain originating in the viscera or muscles. Many drugs are employed for this purpose. The most frequently used counterirritant is heat, applied in the form of the *hot water bottle* or *electric heating pad.*

The following drugs are employed as counterirritants and are representative of this class of pharmacologic agents: black mustard, camphor, chloroform, methyl salicylate, and iodine. Pharmaceutical preparations of these drugs which are suitable for local application to the skin are described in the following section.

### Mechanism of action of counterirritants in pain relief.

The irritant drugs, when applied to the skin, elicit an increase in the circulation in the area of application. A vasodilatation is produced. There is a feeling of warmth in the area and a subjective sensation of comfort.

The local irritation resulting from the stimulation of the cutaneous nerve endings may relieve pain originating in the viscera or muscles. Several theories have been proposed to explain this action of the irritant drugs. There is no unanimity of opinion, however, regarding the mechanism of action of the counterirritants. Their action may be classified and outlined as follows:

1. Stimulation of sensory nerve endings produces a vasodilatation in a remote area because of reflexes acting through the cerebrospinal axis.
2. Stimulation of sensory nerve endings produces a localized vasodilatation of the skin owing to axon reflexes.
3. Counterirritants may produce a summation of pain stimuli.

**Reflexes mediated through the cerebrospinal axis** originating from sensory nerve fiber stimulation produce efferent stimuli that elicit a vascular response in the viscera. The afferent sensory nerve fibers from the skin synapse in the cord with efferent vasomotor fibers to the viscus. For example, stimulation of the skin by a counterirritant will increase the number of afferent stimuli to the same level of the spinal cord in which there are synapses with the efferent fibers supplied by that area of the cord. The blood vessels of the organs innervated by this area of the cord may thus be dilated by this reflex action.

**Axon reflexes.** Bayliss in 1902 postulated a theory known as the *antidromic theory* to explain the vasodilatation observed in the "flare" reaction obtained by stroking the skin. The physiologic flare response of the skin is abolished by local anesthetics. It is not affected, however, by sectioning of the sensory nerves. It appears, therefore, that the response is dependent upon the integrity of the terminal branches of the sensory nerves. The spinal synapses are not involved, and it is believed therefore to be an *axon reflex.* Since the impulse in this instance is mediated in a direction opposite to the usual dromic impulse, the reflex mechanism is referred to as *antidromic.* According to this conception, the mechanism of action of the skin irritants in relieving deep-seated visceral pain requires the sensory nerves to be in direct nervous connection with the nerve network of the arterioles. For example, stimulation of the sensory nerves of the skin by a counterirritant would cause a stimulus to pass along the nerves and then to the branches of the arterioles, with a subsequent diffuse vasodilatation. Indeed, the studies of visceral sensations suggest such a possibility.

The question is far from settled, and it is clear that further investigation is necessary for a complete elucidation of the nature of the vasodilator fibers in the posterior roots.

**The summation of pain stimuli.** The classical signs of skin inflammation are *heat sensations, redness, pain, swelling,* and eventually *impaired skin function.* As indicated previously, these signs represent an increasing degree of irritation and can be produced by the skin irritants. In producing these effects, the counterirritants may also act to relieve visceral pain by causing intense stimulation of the areas of consciousness in the brain, to the partial exclusion of the pain stimuli. According to this conception of their action, stimuli originating in the viscera or muscles are transmitted over fibers in a common pathway along with sensations from the skin. Stimuli from viscera or muscles are referred to the same area of the cord as are stimuli from the skin. If the intensity of stimulation from the skin is increased by the irritant action of the drug, the character of the visceral or muscle pain becomes modified. With intense skin stimulation the visceral pain stimuli may be partially or completely obliterated insofar as the sensorium is concerned. The patient's attention is diverted from the diseased area by the application of the counterirritant drug.

Undoubtedly the action of counterirritants in relieving pain has a strong psychic component. Their therapeutic merits, based upon established empirical observation, are well recognized. Whatever their mechanism of action, the judicious use of the counterirritant drugs has a place in medical practice.

### Relief of referred pain.

As a general rule, when the sensory nerves from an internal organ are excited by inflammation, the pain is referred not to the diseased part but to the area of the skin innervated by the spinal nerve originating from the same area of the cord. Sensations of pain cannot be elicited from the viscera by the usual means of stimulation. The studies of Head (1894), Mackenzie (1909), and others have provided the concept of referred pain. The source of the stimulus and the apparent site of the pain or tenderness may be some distance apart. For example, in peptic ulcer, impulses may be carried to the sympathetic ganglia and a sensitive area may be set up in the segments of the spinal cord where the nerve enters. A sensation of pain may thus be localized in the skin of the epigastric region. This area is supplied by sensory spinal nerves originating in this segment of the cord.

In angina pectoris the classical symptom of referred pain to the left shoulder radiating down the ventral surface of the arm has its origin in the heart.

In neuralgias the pain may be referred to a skin area, and the part may even become tender and inflamed. For example, a carious tooth may produce facial neuralgia by stimulation of the trigeminal nerve. By the application of a counterirritant to the appropriate skin site, the pain may be relieved.

In general, sensations which reach the cortex from areas which only infrequently produce stimuli are referred to bodily areas where sensory innervation is more abundant. In the brain, visceral sensations are very imperfectly localized; sensations from the skin are accurately located. Therapeutic advantage is taken of this physiologic fact in the topical use of the counterirritant drugs in the relief of pain resulting from stimuli originating in viscera or muscle.

### Therapeutic use.

The counterirritants have been used most successfully in *neuralgias, rheumatoid arthritis, bursitis, myositis,* and *integumental pain.*

**Mustard Plaster, N.F.,** is a uniform mixture of powdered black mustard (*Sinapis nigra*) deprived of its fixed oil and admixed with a rubber adhesive and spread on cotton cloth or paper. Before application the plaster is soaked in warm water for approximately 2 minutes. Generally a mustard plaster is allowed to remain in place for 15 minutes. A longer period of application may produce painful blistering. For therapeutic results only rubefaction is necessary.

**Methyl Salicylate, U.S.P.,** is a colorless, volatile oil having the characteristic odor of wintergreen. When rubbed on the skin it produces a mild degree of irritation and is absorbed to an appreciable extent. It is most frequently used in the treatment of arthralgias and neuralgias as a counterirritant. Because methyl salicylate has a candy-like odor, it is frequently the cause of poisoning in children. Salicylate poisoning is discussed on page 455.

**Iodine, Tincture U.S.P. (mild tincture of iodine)** when applied to the skin acts as an irritant. It is employed as a counterirritant by repeated application to the skin. Iodine is absorbed directly through the skin, and care must be exercised lest too large an area be covered and toxic amounts of iodine be absorbed. In addition, if iodine tincture is applied in too high a concentration for too long a period or if the skin is kept covered, severe vesication may be produced. True hypersensitivity to iodine tincture is frequently encountered. It should be used cautiously as a counterirritant.

**Camphor Liniment, N.F., Chloroform Liniment, N.F.,** and **Camphor and Soap Liniment, N.F.,** are mild-acting rubefacients that have a limited place in therapeutics as counterirritants.

### REFLEX MEDULLARY STIMULANTS

The reflex medullary stimulants produce stimulation of the sensory nerve endings that *reflexly* stimulate the respiratory and vasomotor centers in the medulla. It is well established that strong sensory stimuli, such as dashing cold water upon the body, produce a temporary arrest of respiration followed by a powerful gasping inspiration and a rise in blood pressure. This is caused by reflex medullary stimulation. Reflex stimulation of the medullary centers may be produced also by the local irritation resulting from the inhalation of ammonia or other irritant gases. The injection of irritating substances parenterally, for example, ether, will reflexly produce vasomotor changes and respiratory stimulation.

In the anesthetized animal, strong stimulation of a sensory nerve trunk can be shown to produce a change in blood pressure, a cardiac acceleration, and an increase in the rate and depth of respiration. In the unanesthetized individual the results of strong sensory stimuli are more pronounced and more complex. Moderate pain may cause a rise in blood pressure and a slight increase in respiratory rate. In an unconscious individual the application of ammonia vapors to the nostrils may, by virtue of their reflex medullary stimulant action, produce an enhancement of respiration and a rise in blood pressure. The results in a person who has fainted may be most dramatic.

The reflex respiratory stimulants are of little value in cases of profound respiratory depression, which occur following overdoses of such drugs as morphine, the barbiturates, or the anesthetics. However, the merits of this type of stimulation must not be overlooked entirely in treating patients in this condition.

### Aromatic Ammonia Spirit, U.S.P.

This is a most useful and effective reflex medullary stimulant. It contains about 2 per cent of total $NH_3$ and approximately 4 per cent of ammonium carbonate in a hydroalcoholic solution of volatile oils. The spirit is a colorless to pale yellow liquid. It emits the characteristic aromatic, pungent odor of ammonia and aromatic oils. In cases of fainting the patient inhales the vapors. An average dose of 2 to 4 ml. diluted with an ounce of water and administered orally is effective in *threatened collapse, fainting,* or *weakness.* The action is upon the esophageal and gastric mucosa as a local irritant which reflexly stimulates the medullary centers.

**Brandy, N.F.,** and **Whiskey, N.F.,** may be employed orally as reflex stimulants.

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# 16

# *Local Anti-infective Drugs*

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This chapter is concerned with those drugs that are used as *antiseptics*, *disinfectants*, *anti-bacterials*, *fungicides*, *parasiticides*, and *antifungal* and *antipedicular agents*. Local anti-infective drugs, or antiseptics, are used by topical application and may be differentiated from the systemic agents described in the preceding chapters. By definition, antiseptics or disinfectants are chemical substances destructive to bacteria and sufficiently noninjurious to the skin and mucous membranes to permit their application locally to specific portions of the human body.

Many antiseptics are toxic if used systemically; poisoning frequently has resulted from their injudicious use. Indeed, our modern chemotherapeutic anti-infective agents were discovered as a result of efforts to prepare nontoxic antiseptics. The history of man's search for potent anti-infective drugs is intimately entwined with the development of modern antiseptic surgical technics. In fact, the development of efficient antiseptics has made possible the spectacular surgical procedures of modern medicine. In preparing the patient for surgery, they are surpassed in importance only by the general anesthetics.

The general intelligence of the laity with respect to the nature of common infection from wounds and minor abrasions has resulted in the widespread use of the local anti-infective drugs. One or more members of this class of compounds may be found in nearly every household medicine cabinet. This is of toxicologic importance, and poisoning with these drugs is considered in this chapter. The physician should know the location of the nearest Poison Control Center which operates under the direction of the National Clearinghouse for such centers in the United States. The nature of this service is described on page 2.

### Historical Development

One of the earliest direct observations of the value of an antiseptic material was made by the young Viennese physician Ignaz Semmelweis. His keen observation in 1844 of the infectious nature of disease and of how a simple antiseptic technic could prevent infection during childbirth permitted him to make a far-reaching discovery. In 1847 Semmelweis instituted the requirement of thorough cleansing of the hands and arms and washing in chlorine water in the maternity ward of the Vienna General Hospital. The students and physicians coming from the autopsy laboratories, who were preparing to deliver the mothers, were required to wash their hands in chlorine water. As a result of this requirement, a dramatic reduction in the incidence of "childbed fever" occurred, with a spectacular decrease in mortality. Without ever recognizing the exact nature of his discovery, Semmelweis had proved that bacteria cause disease years before Robert Koch and Louis Pasteur laid the foundations of the science of bacteriology. Unwittingly he had selected an active anti-infective agent, chlorine water.

Pasteur was the first to suggest that as each variety of fermentation originated by the action of a specific ferment, so in the case of disease the "infection" depended upon the presence of a specific microbe. His generalization with respect to the bacterial diseases proved to be correct.

Joseph Lister realized the significance of the observations of Pasteur and applied to surgery the idea of *disinfection*. In 1867 he announced his method of sterilization of wounds, bandages, and surgical dressings. Carbolic acid was employed by Lister as a germicide. The substance was used very liberally because at that time it was believed to be necessary to kill every bacterial organism. Later, by gradual improvement of his methods, Lister introduced *aseptic surgery*. By the exclusion of bacteria from wounds and by scrupulous cleanliness in the operating theatre and the sterilization of instruments, he demonstrated that corrosive germicides were not necessary. The technic at that time was known as *Listerism*. It is recognized today that surgical sterility is not necessarily absolute sterility. An object may be surgically sterile and still contain on its surface the spores of nonpathogenic yeasts, molds, or various nonpathogenic bacteria.

It was said of Joseph Lister that he saved more lives by the introduction of his system of aseptic surgery than all the wars of the nineteenth century together had sacrificed. The student should read Lister's original paper, reprinted in *The American Surgeon*, **10:** 1127, 1954.

### Classification

The drugs that are employed as local anti-infective agents, or, as they are commonly referred to, antiseptics, may be classified in numerous ways. For convenience they will be discussed in this section as follows:

1. Protoplasmic poisons
2. Oxidizing agents
3. Cationic detergents
4. Antiseptic dyes
5. Miscellaneous anti-infectives

### Definition of antiseptics.

Agents known as antiseptics, germicides, sanitizers, disinfectants, fungicides, bactericides, and sporicides are defined in legal terms. These drugs sold in interstate commerce in the United States must be registered with the U. S. Department of Agriculture and meet the requirements of the Federal Insecticide, Fungicide and Rodenticide Act.

### Evaluation

Unfortunately, present scientific knowledge does not provide a single test capable of evaluating an antiseptic. Several criteria are used. These involve both *in vitro* and *in vivo* measurements. Reddish (1957) has outlined methods for testing antiseptics. These involve highly specialized bacteriologic technics. Skin disinfectants are evaluated by comparison with phenol as a standard agent, using both vegetative bacterial cells and clostridial spores. This permits the determination of the *phenol coefficient*. In addition, the germicidal efficiency under conditions simulating actual use is determined. Tissue toxicity is determined by measuring the degree of irritation to the skin and mucous membranes produced by anti-infective substances, and tests have been devised to assay the *degree* of sensitization. Allergic responses elicited in the skin of animals by the agent, when applied in the recommended dilutions, may be evaluated. Subacute and chronic toxicity tests in animals are required for certification of antiseptics (Duffett *et al.*, 1961).

Most authorities agree that the testing methods available at the present time are not entirely adequate, and that while the potential value of an antiseptic may be determined by these methods, the need for improved technics is great.

Because so many methods have been used by different workers in evaluating antiseptic potency and tissue toxicity, the specific technics are usually described for each of the newer anti-infective agents in the section devoted to the particular drug.

### Protoplasmic Poisons

Many chemicals are toxic to cell protoplasm. In certain instances they may possess a specific affinity and toxicity for microorganisms of a special type, *e.g.*, the antimalarial drugs. In other cases the effect upon cells may be nonselective, and cells of the host as well as invading bacteria may be killed. Protoplasmic poisons belong to the latter category. For this reason these agents must be used judiciously as antiseptics.

The salts of mercury and silver dissolved in water have been used as antiseptic solutions for many years. Today these substances have to a large extent been replaced by less toxic organic chemicals.

### Mercury salts.

Mercury bichloride solutions are antiseptic. They have a limited bactericidal activity for nonsporulating organisms. These solutions do not kill bacterial spores effectively even after several hours of exposure. The presence of albuminous material decreases their activity. Mercuric chloride solutions act by combining with sulfhydryl groups of bacterial protoplasm, and their anti-bacterial action is neutralized by compounds containing SH groups, *e.g.*, glutathione.

Bichloride of mercury solutions are used for skin disinfection and disinfection of instruments, excreta, and discharges. Solutions of mercuric chloride are useful in disinfecting contaminated glassware and laboratory apparatus. Aqueous solutions of 1:100 to 1:10,000 dilution are generally employed. A solution of mercuric chloride 1:1000 in 25 per cent alcohol is a cheap, efficient germicide.

**Mercury Bichloride, N.F. (corrosive sublimate)** is a heavy, odorless, crystalline or white, powdery substance. It is soluble in water. The salt dissociates to a relatively small degree. The addition of sodium chloride, ammonium chloride, or citric acid increases the solubility of mercuric chloride. These substances are employed as excipients in the official tablets, *mercury bichloride large poison tablets.* These tablets are designed to be dissolved in water to provide a 1:1000 solution. One tablet is dissolved in 500 ml. of water. The tablets are of a distinctive color, not white; they must be of an angular or irregular shape, not discoid, to comply with the official standards.

**Yellow Mercuric Oxide, N.F.,** is a yellow-orange, heavy, impalpable powder. It is insoluble in water. This compound of mercury is employed almost exclusively in medical practice as the official ointment, *Yellow Mercuric Oxide Ointment, N.F.*, which contains 1 per cent HgO in a white ointment base. It is used mainly for application to the eye as a mild antiseptic ointment in conjunctivitis, blepharitis, and styes.

**Toxicity.** The soluble salts of mercury formerly were very common causes of poisoning. The tablets of bichloride of mercury have been taken frequently by mouth, accidentally or purposefully, hence the restrictions that the official standard has established regarding the shape of these tablets.

Absorption of mercury compounds can be achieved directly through the skin. Metallic mercury is absorbed readily from skin surfaces, and hypersensitivity reactions to mercury compounds are frequently observed. Skin absorption of mercury compounds is a frequent source of industrial poisoning. Mercury vapor poisoning has resulted from the inhalation of the readily volatilized metal.

**Acute mercury poisoning,** most frequently encountered in medical practice, results from the ingestion of bichloride of mercury. The soluble salts of mercury are corrosive to the mucous membranes of the alimentary tract. The local irritation causes vomiting, abdominal discomfort, and bloody diarrhea. Absorption of small quantities may produce irreversible kidney damage. The tubule cells disintegrate, and uremic poisoning results. The endothelium of the glomerular capillaries may also suffer degenerative changes.

Early deaths from acute mercury poisoning are usually the result of severe kidney damage. Within 24 to 48 hours' albuminuria develops, the volume of urine decreases, and acute interstitial nephritis may eventually terminate in death within a period of a week. Ulceration of the intestinal tract may occur, and hepatic degeneration has been reported. There is usually a decrease in blood chlorides and an increase in nonprotein nitrogen of the blood. A toxic dose of 0.1 gm. of mercuric chloride has caused severe poisoning; 0.5 gm. may be fatal. The degree of toxicity is directly related to the amount absorbed from the gastrointestinal tract. It is generally stated that if 1 gm. is taken by mouth and the individual is not treated by the administration of antidotes within 15 minutes, death will result from renal failure after a period of days. If vomiting occurs promptly after the administration of soluble mercury salts, the prognosis is good. The $Hg^{++}$ ion is toxic to the myocardium, and with high concentrations in the blood, signs of cardiac toxicity may be observed.

In recent years the number of deaths resulting from accidental poisoning by mercury and its compounds has decreased. In 1959 only 11 deaths were reported by the National Clearinghouse for Poison Control Centers for the United States.

*Treatment.* Obviously, because of the nephrotoxic nature of the mercuric ion, an important step in the treatment would be the removal of as much of the salt as possible before absorption. Furthermore, the feeding of quantities of egg albumin and milk is advantageous, because these substances combine with the mercuric ion and form insoluble protein combinations. Intravenous dextrose remains as the mainstay to combat the anuria of bichloride of mercury poisoning.

The prompt oral administration of milk, egg white, or other albuminous substances fixes the mercuric ion in the form of the relatively insoluble proteinate. The patient must be made to vomit. The intravenous administration of a 50 per cent glucose solution may assist in combating the threatened kidney damage. The most effective systemic antidotes in the treatment of acute mercury poisoning are dimercaprol and penicillamine. Symptomatic treatment to relieve the distressing diarrhea and pain is usually indicated.

**Chronic mercury poisoning** may occur in individuals exposed to mercury compounds in industry or in the home. Absorption may be slow, and since the source is frequently obscure, the symptoms in the individual may present a misleading clinical picture. Mental and central nervous system changes may be encountered in persons exposed to daily inhalation of elementary mercury vapor. Gingivitis is perhaps the most typical symptom of chronic poisoning. Poor dental hygiene under these conditions may result in the loosening of the teeth. Blackening of the gingival margins is characteristic and is observed in other types of heavy metal poisoning. Salivation and tenderness of the tongue and gums, a metallic taste, and a fetor of the breath are characteristic signs. Constipation or diarrhea, anemia, and gradual loss of body weight are frequent symptoms of chronic poisoning. Nephritis or hepatitis has resulted from prolonged chronic exposure to mercury compounds. A diagnosis can only be confirmed by demonstrating excessive amounts of mercury in the urine.

*Treatment* of chronic poisoning is largely symptomatic after removal of the source of mercury intoxication. Hygiene of the mouth is important in relieving the symptoms of the buccal cavity. Dimercaprol or penicillamine may be used in the treatment of acute or chronic mercury poisoning (see page 950).

**Merbromin, N.F. (Mercurochrome)** is the disodium salt of 2,7-dibrom-4-hydroxymercurifluorescein.

A 2 per cent solution of merbromin in water applied to the skin, wounds, or mucous membranes is antiseptic and nonirritating.

**Thimerosal, N.F. (Merthiolate)** is sodium ethylmercurithiosalicylate.

Solutions of thimerosal in water are germicidal for many nonsporulating organisms. Applied topically to the skin and mucous membranes, solutions of this antiseptic are nonirritating. Tincture of thimerosol is a 1:1000 solution of the drug in alcohol-acetone-water. The tincture is applied to the intact skin preoperatively for disinfection. Aqueous solutions of 1:1000 are employed for disinfection of instruments, wounds, and denuded skin surfaces. Antiseptic solutions of thimerosal may cause skin sensitivity reactions.

**Nitromersol, N.F. (Metaphen)** is the anhydride of 4-nitro-3-hydroxy-mercuri-*ortho*-cresol. It is insoluble in water.

When nitromersol is dissolved in aqueous solutions in the presence of alkali, the anhydride ring opens, forming the hydroxy-mercury salt. Solutions for germicidal and general surgical antiseptic use are prepared with the aid of sodium hydroxide. The aqueous solutions of 1:1000 and 1:5000, prepared with buffer salts, are relatively nonirritating when applied to the skin or mucous membranes. Tincture of nitromersol is a 1:200 solution in a mixture of acetone, water, and alcohol.

### Silver salts.

The soluble salts of silver ionize in water to yield solutions that are strongly astringent and antiseptic in high dilutions. These effects are produced by the silver ions.

**Silver Nitrate, U.S.P.,** is a colorless or white, crystalline, water-soluble salt that darkens upon exposure to light. A dilution of 1:1000 of silver nitrate is strongly antiseptic in the absence of protein material. The antiseptic action of this solution is accompanied by irritation, astringency, and corrosion.

Solutions of silver nitrate are commonly employed as an antiseptic in the eye. Gonococci are susceptible to silver nitrate solutions, and many states legally require the use of these solutions for the prophylaxis of *ophthalmia neonatorum*. A 1 per cent solution is instilled into the conjunctival sac. This solution is official under the name of Silver Nitrate Ophthalmic Solution, U.S.P. It is supplied in small wax ampules containing about 0.5 ml. There has been a trend in recent years to replace silver nitrate solution by penicillin solution for the prevention of ophthalmia neonatorum.

**Toughened Silver Nitrate, U.S.P.,** or fused silver nitrate, is applied topically as a caustic. The merits of the judicial use of a simple chemical cauterizing agent of this type are frequently overlooked in favor of electric cauterization. This form of chemical cauterization is used in the treatment of cervical erosion.

**Mild Silver Protein, N.F.,** occurs as a dark brown or almost black powder, shining scales, or as a granular substance freely soluble in water to yield a colloidal solution. Solutions of silver protein are decomposed by light; for antiseptic purposes the solution must be freshly prepared.

**Toxicity.** The salts of silver do not produce acute systemic poisoning even when large doses are taken by mouth. The precipitation of the metal ion by chlorides and by protein prevents the absorption of a sufficient amount to produce acute generalized poisoning. Egg albumin and sodium chloride solution administered by mouth are effective antidotes in cases of oral poisoning.

The long-continued use of a silver preparation may induce chronic intoxication. A bluish black discoloration of the skin known as *argyria* is produced. This distressing condition probably results from the deposition of organo-silver compounds in the sweat glands of the skin, where the action of sunlight reduces the silver salts to dark-colored compounds. The condition of argyria persists indefinitely, and there is no known treatment.

**Dichloroacetic acid (bichloracetic acid)** is a corrosive liquid with a pungent odor. It is used as a cauterizing agent for tissue destruction and sterilization in cervicitis and for the removal of epithelial scars and benign, pigmented skin discolorations. The acid is applied undiluted with a pointed applicator stick.

### Iodine preparations.

In this section only those iodine preparations that are employed therapeutically as anti-infectives will be discussed.

Elementary iodine dissolved in a hydroalcoholic solvent is one of the most commonly employed topical antiseptic solutions. Its chief use is as a disinfectant of the patient's skin preparatory to surgery. Iodine tincture has great penetrating power and retains most of its antiseptic activity in the presence of foreign matter, skin exudates, and serous fluids. After application the area is generally cleansed with 70 per cent alcohol.

Aqueous solutions of iodine contain elemental iodine ($I_2$), triiodide ion ($I_3^-$), hypoiodous acid (HIO), hypoiodite ion ($IO^-$), and iodate ion ($IO_3^-$). The relative concentrations of these substances are functions of the pH, age of the solution, and other factors. Hypoiodous acid (HIO) exhibits the greatest antimicrobial activity, followed by $I_2$; the least activity is shown by the triiodide ion ($I_3^-$). Germicidal activity is related to the iodination rate of proteins. Toxicity is greatest with the least potent anti-bacterial constituent $I_3^-$. The least toxic HIO is also the most potent antiseptic element in the solution.

**Iodine Tincture, U.S.P.,** is a 2 per cent solution of iodine and 2.4 per cent sodium iodide in 50 per cent alcohol. It is a transparent liquid with a reddish brown color. It was formerly known as *mild surgical tincture of iodine*. From the standpoint of economy and dependability, this antiseptic solution is perhaps the most satisfactory.

**Action on the skin.** When applied to the skin, tincture of iodine produces a characteristic brown stain. On the unbroken skin it causes reddening and irritation, with vasodilatation of the cutaneous vessels. When applied repeatedly, the degree of irritation may become intense, with blister formation and desquamation of the epidermis. In the presence of such a degree of irritation, an appreciable amount of iodine may be absorbed. It must be applied cautiously because it is corrosive, and severe tissue damage may result from application to a large area.

**Strong Iodine Solution, U.S.P. (Lugol's solution)** is a 5 per cent solution of iodine made soluble by the presence of 10 per cent potassium iodide. The solution has a deep brown color and the odor of iodine. The aqueous solution of iodine is antiseptic, although it is not generally used as a germicide. This solution is employed for oral administration of iodine in goiter (see page 889).

**Toxicity.** Tincture of iodine is commonly present in the home. Accidental or suicidal poisoning with this substance sometimes occurs. The symptoms produced are severe gastrointestinal pain, vomiting, and diarrhea, with prostration, depression, and collapse. Iodine taken in this form is not as poisonous as is generally believed. Most of the effects are confined to the gastrointestinal tract because the iodine that is absorbed enters the circulation as the relatively nontoxic iodide. Corrosion of the gut may be the cause of death. Those individuals that succumb usually die within 24 to 48 hours of shock, circulatory collapse, or pneumonia.

In the treatment of oral iodine poisoning, starch suspension, demulcent fluids, or 1 per cent solutions of sodium thiosulfate are used. Sodium thiosulfate combines chemically with the elementary iodine, forming the relatively innocuous sodium iodide and sodium tetrathionate.

Starch paste has demulcent properties and soothes the irritated mucous membranes, as well as combining with the iodine to form iodized starch. Gastric lavage is important in order to remove the compounds formed, but care must be exercised to avoid perforation of the stomach wall. The dehydration may be relieved by intravenous saline. Supportive measures may be advisable in collapse, and shock therapy may be instituted if this condition seems imminent.

**Organic compounds of iodine. Iodoform, N.F.,** is a lemon yellow, water-insoluble powder, with a characteristic penetrating odor. It is usually applied as an antiseptic dusting powder.

*Povidone-iodine* (*Betadine*, *Isodine*) is an organic iodine complex formed by reacting iodine with polyvinylpyrrolidone polymer. The substance is water-soluble, and when a solution is used as an antiseptic, the complex breaks down on contact with the skin or mucous membranes and free iodine is slowly released. The 1 to 1.5 per cent solution does not produce local stinging or irritation.

The desirable properties of iodine as a potent germicide and the advantages of its combination with a highly anti-bacterial, surface-acting quaternary are stressed in a study conducted by Frisch and associates (1958) to evaluate a number of antiseptic agents. Their report indicated that iodine preparations of this character were superior to soap, hexachlorophene scrubs, and cationic agents alone when employed as skin disinfectants.

*Undecoylium chloride-iodine* (*Virac*). By combining the quaternary compound acylcolaminoformylmethyl-pyridium chloride with iodine, a complex is formed which exhibits germicidal properties. The acyl group of the quaternary is a mixture containing from 8 to 14 carbon atoms.

The cationic detergent properties of this preparation, combined with the antimicrobial activity of the elementary iodine which is slowly released upon contact with the skin and mucous membranes, provides an efficient topical antiseptic. The iodine complex is water-soluble, and a protein-iodine precipitate is not formed on wound surfaces. When used in a 0.2 per cent concentration as available iodine in aqueous solution, the preparation does not cause stinging or irritation to skin or mucous membranes. Krippaehne and Frisch (1959) found this preparation to be effective as a preoperative scrub. It appears to be as efficient as hexachlorophene preparations. Repeated contact with the detergent-iodine solution caused drying of the skin and a low incidence of sensitivity reactions (maculopapular rash). As a topical antiseptic the solution appears to be useful.

**Chlorine preparations.** A solution of elementary chlorine in water has been used for years as an antiseptic, to arrest the growth and development of bacteria, and to destroy foul odors.

Sodium Hypochlorite Solution, N.F., contains 5 per cent NaOCl. It is a clear, pale, greenish yellow liquid having the odor of chlorine. It is diluted 10 times for skin or wound germicidal use. Diluted Sodium Hypochlorite Solution, N.F., known also as Modified Dakin's solution, is an aqueous solution of chlorine compounds containing approximately 0.5 per cent NaOCl. It is a colorless liquid having a slight odor of chlorine.

### Phenol, cresol, and related compounds.

**Phenol, U.S.P.,** is a colorless, crystalline compound having a characteristic odor. It is soluble in water to the extent of approximately 6 per cent. Its solutions gradually darken upon exposure to air and light. It is commonly called *carbolic acid*.

*Liquefied Phenol, U.S.P.*, is phenol maintained in a liquid condition by the presence of 10 per cent of water. When freshly prepared it is a colorless liquid; it may develop a pink to red tint upon exposure to air or light. It is miscible with alcohol or glycerin but not with water.

*Action on cell protoplasm.* In dilutions of 1:500 to 1:1000, phenol exhibits a characteristic coagulating action on protoplasm. Low forms of life succumb to this action. The coagulum of protein causes a fixation of the protoplasm of the cell. The coagulum formed is not like that formed by mercuric chloride, which is a definite chemical combination and cannot be washed out. Phenol escapes from its combinations with cell proteins and hence has greater penetrating power. In fact, phenol and related cresols will dissolve many proteins. It is assumed that this property is related to the anti-bacterial effect of these agents in interfering with bacterial enzyme systems.

Higher dilutions of phenol denature the protein of cells without coagulation. It is not an effective germicide because 1 per cent solutions in water are required to kill most of the common pathogenic organisms. Spores are particularly resistant to phenol. Aqueous solutions of 0.5 to 1 per cent are bacteriostatic and fungicidal.

**Phenol coefficient.** Phenol has been the standard of comparison for other bactericidal drugs for many years. A standard strain of microorganism should be killed by a dilution of 1:90 of phenol in 10 minutes. Adopting this *in vitro* test as a standard, an unknown antiseptic may be evaluated. The antiseptic potency is designated as the *phenol coefficient.* Most modern antiseptics have phenol coefficients of from 500 to 1000, indicating that they are from 500 to 1000 times more potent than phenol.

The method of evaluating anti-bacterial compounds on the basis of their phenol coefficient is unreliable in assessing their value as antiseptic drugs. The toxicity to the animal organism of the substance in question is of paramount importance and must be given due consideration. *In vivo* experiments are essential in exploratory work with new compounds; in fact, the sulfonamides would not have been discovered had it not been for *in vivo* tests in mice.

Methods have been devised to assay the skin germicidal efficiency of an antiseptic solution under conditions simulating the actual use of the preparation. In addition, germicides have been evaluated for their tissue toxicity by measuring the effects upon the viability of chick heart tissue fragments cultivated *in vitro.* In this test preparation, phenol is twice as toxic to tissue cells as to bacterial cells, while iodine has the least tissue toxicity and the greater antiseptic potency. The merits of *in vivo* testing technics were stressed in the report of the discovery of the potent quaternary antiseptic triclobisonium chloride (Triburon) by Grunberg and Schnitzer (1959).

*Action on the skin.* A 5 per cent solution of phenol applied to an open wound produces immediate local anesthesia. There is a fixation of protoplasm, and exposed sensory nerve endings are killed. Tissue necrosis develops at the site of application after prolonged contact. When applied to intact skin, liquefied phenol coagulates protoplasm and blanches and hardens the skin, producing an area of anesthesia. Later a reddish brown stain develops that remains until the epidermis is desquamated. Severe burns may be produced by phenol. The penetrating power of phenol applied topically is sufficiently great to produce systemic effects.

Deichmann *et al.* (1952) found appreciable absorption of phenol when a 2 per cent phenol preparation in calamine lotion or a 4.75 per cent phenol preparation in aromatized liquid petrolatum was applied topically. The material was applied to 75 per cent of the body surface of each of a group of male volunteers. After repeated applications the free blood phenol rose from a control value of 0.15 to 0.4 mg./100 ml. of blood. There was an accompanying rise in conjugated blood phenol. They warn that while the application of phenol preparations to the skin is considered safe, toxic effects may ensue if the rate of absorption exceeds the capacity of the conjugating detoxifying mechanism.

*Phenolated Calamine Lotion, U.S.P.*, containing 1 per cent phenol, is employed to relieve itching of the skin in mild dermatologic lesions. The presence of phenol in the lotion probably renders it mildly antiseptic.

**Cresol, U.S.P.,** is a mixture of 3 isomeric cresols obtained from coal tar. It is colorless or brownish yellow to pink, becoming darker with age or exposure to light. Cresol has a phenol-like, characteristic odor. It is soluble in water to the extent of approximately 2 per cent. Cresol is a protoplasmic poison like phenol, but it is less toxic. Cresol was introduced into medicine as an antiseptic, and it is still used as a crude disinfectant.

**Resorcinol, U.S.P.,** is a white, crystalline powder with a faint characteristic odor. It acquires a pink tint upon exposure to light and air. It is soluble in an equal part of water. Resorcinol possesses the germicidal properties of phenol. Its anti-bacterial effect is enhanced by substitution of an alkyl grouping or a halogen atom in the ring. It is less toxic than phenol and less irritating and caustic. *Compound Resorcinol Ointment, N.F.*, is a 6 per cent ointment of resorcinol; it is employed on the skin as a local keratolytic agent. Some dermatologists consider resorcinol and its preparations worthless as antiseptics and antifungal agents.

**Hexylresorcinol, U.S.P.,** is a white, crystalline, insoluble powder with a faint odor. It acquires a brownish pink tint on exposure to light and air. The use of hexylresorcinol as an anthelmintic is discussed on page 188.

A solution of hexylresorcinol 1:1000 (S.T. 37) is employed as a nontoxic, nonirritating, odorless, and stainless local antiseptic.

**Thymol, N.F.,** is a colorless, crystalline alkyl derivative of cresol with an aromatic, thyme-like odor. It is soluble in water to the extent of 0.1 per cent. A crystal is commonly used as a preservative for urine specimens. An alcoholic solution in 1 to 2 per cent concentration is a weak fungicide. Its use as an anthelmintic is discussed on page 188.

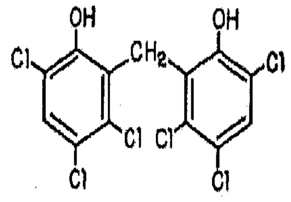
**Toxicology of phenol, the cresols, and related compounds.** Acute suicidal or accidental poisoning with these compounds occurs occasionally. These poisonings will be considered as a class.

When taken orally phenol produces a burning pain in the mouth and throat. The characteristic odor, the whitened lips and mouth, depression, and weakness are diagnostic signs. Nausea, salivation, vomiting, abdominal pain, and vertigo may be evident. The pulse and respiration are first accelerated, then irregular, feeble, and intermittent. The voided urine becomes black upon standing. The individual may be pale, with a clammy skin and face. Collapse, followed by coma and death from respiratory failure, has resulted from doses greater than 10 gm. Cresol, creosote, guaiacol, and the commercial saponated cresols, *e.g.*, Lysol, produce essentially the same symptoms of poisoning but to a lesser degree.

**Treatment of phenol poisoning.** Gastric lavage with warm water containing a demulcent may be the most satisfactory oral antidote. Glycerin and alcohol are excellent solvents for phenol, but they should not be used in a lavage when phenol has been swallowed, since they will promote its absorption. Deichmann *et al.* (1952) found from their study of phenol poisoning in rabbits that prompt administration of a large volume of warm salt water was very efficacious in removing the phenol from the stomach. The evacuation of the stomach should be effected by mechanical means. Emetic drugs are to be avoided. The administration of 50 ml. of castor oil will help reduce the injury to the gastrointestinal tract. If a stomach tube can be passed without injury, gastric lavage with warm water is the most satisfactory means of removing the phenol. Prompt gastric lavage is the most important factor in saving the life of the patient. Respiratory stimulants are used to combat a failing respiration. The treatment otherwise is symptomatic.

External phenol or cresol burns may be treated very satisfactorily by gentle lavage with large quantities of vegetable oil or alcohol. In the case of extensive phenol burns, the area involved should be washed free of phenol by a virtual flood of water. It is possible to remove almost all superficial phenol by repeated washing with water. The subsequent application of an oil dressing is desirable.

**Hexachlorophene, U.S.P. (pHisoHex, Surgi-Cen, Surofene, Gamophen)** may be considered a diphenol. This substance is 2,2′-dihydroxy-3,5,6,3′,5′,6′-hexachlorodiphenylmethane.



Hexachlorophene, U.S.P.

Hexachlorophene is a white, crystalline powder, insoluble in water. It is germicidal for gram-positive bacteria. Gram-negative organisms are much more resistant to its action. *Hexachlorophene Liquid Soap, U.S.P.*, is used as an antiseptic skin cleansing agent. Repeated scrubbing of the skin with a hexachlorophene preparation results in the reduction of the number of skin-surface bacteria. The most satisfactory clinical use of these preparations is obtained by daily application. Applied as a soap, a detergent cream, or in an oil base, hexachlorophene inhibits the growth of microorganisms which may be normally present on the skin. Hexachlorophene is useful as a prophylactic agent in decreasing the incidence of pyogenic skin infections, *e.g.*, furuncles, carbuncles, impetigo, and seborrheic dermatitis.

Preparations such as pHisoHex, containing 3 per cent hexachlorophene, are used widely for preoperative cleansing of the skin of the patient and for cleansing superficial wounds. Its potent antiseptic properties permit a 2-minute preoperative scrub of the operator's hands. On scrubbed areas a condition approximating sterility and inhibited growth of bacteria is said to be maintained for many hours. It should be pointed out, however, that the antiseptic power of hexachlorophene is considerably reduced in the presence of blood and other organic matter. The area treated with the hexachlorophene preparation should not be washed with alcohol or other organic solvents, since this will remove the adsorbed antiseptic material.

A desirable feature of hexachlorophene is its bland, nontoxic character. The preparations dry the skin upon repetitious use but are not locally irritating. Hypersensitivity reactions to hexachlorophene have been frequently reported.

One of the unanswered questions regarding the use of hexachlorophene as an antiseptic is the development of a resistant bacterial flora. The bacteriologic tests that have been reported do not indicate the development of resistant bacteria. Mudd (1958) and others have stressed the value of anti-bacterial detergents containing hexachlorophene in the prevention and control of staphylococcal infection centered around hospital personnel. The program for the control of antibiotic-resistant staphylococci includes the use of scrubbing with hexachlorophene detergents by attendants and patients. Hexachlorophene preparations are very effective cleansing and anti-bacterial agents for hospital use, in the physician's office, and in the home.

**Bithionol, U.S.P. (Actinol, Actamer)** is 2,2′-thiobis(4,6-dichlorophenol). This substance is a white, crystalline, water-insoluble powder. As a soap-compatible bacteriostatic agent, this chlorinated thiodiphenol is used in a 2 per cent concentration in bar soap. Its action and uses resemble those of hexachlorophene.

### OXIDIZING AGENTS

Chemical substances which readily yield oxygen in the presence of tissue elements are useful as germicidal agents. In this section those oxidizing agents suitable for therapeutic use as antiseptics will be considered.

#### Hydrogen Peroxide Solution, U.S.P.

This colorless liquid is an aqueous solution containing 3 per cent $H_2O_2$. Hydrogen peroxide liberates oxygen when in contact with the broken skin or mucous membranes. In the presence of the enzyme catalase, the molecule undergoes decomposition with the evolution of oxygen. The solution is a very poor antiseptic; its chief value seems to be as a cleansing agent and deodorant.

#### Potassium Permanganate, U.S.P. ($KMnO_4$).

This is a strong oxidizing agent, even in high dilution. In contact with organic matter, $KMnO_4$ liberates oxygen. Bacteria are inhibited or destroyed by freshly prepared, dilute solutions.

#### Sodium Perborate, N.F. ($NaBO_2 \cdot 4H_2O$).

This white, crystalline powder is odorless and stable in the dry state. It is soluble in water (1 in 40); the solution decomposes into sodium metaborate and hydrogen peroxide, gradually evolving oxygen. Sodium perborate is generally not prescribed in solution. A teaspoonful in a glass of water is used as an antiseptic mouth wash. In contact with mucous membranes, it rapidly liberates oxygen. The solution has a saline, alkaline taste. It is extensively employed in the local treatment of *glossitis*, *gingivitis*, and *stomatitis*. The long-continued use of this preparation is not without hazard, and damage to the mucous membranes of the oral cavity may result. Alone or combined with an equal part of potassium chlorate, sodium perborate is used in the treatment of Vincent's infection. When used in oral hygiene, the solution must not be swallowed.

#### Metal peroxides.

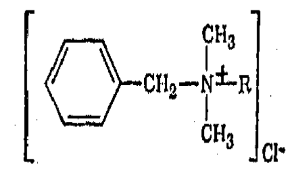
These compounds are oxidizing agents and liberate their oxygen in contact with tissues. Certain members of this group possess a limited solubility. The degree of ionization of the hydroxide formed determines the extent of irritation. Thus the uses of sodium peroxide ($Na_2O_2$) are limited by the strong base formed when it dissolves in water. This preparation is used as a paste or soap in acne and to remove comedones.

**Medicinal Zinc Peroxide, U.S.P.,** consists of a mixture of zinc peroxide, zinc carbonate, and zinc hydroxide. It contains approximately 45 per cent $ZnO_2$. It is a fine, white odorless powder, insoluble in water. For medicinal use the powder is sterilized in a dry oven for 4 hours at exactly 140°C. A smooth, creamy suspension (40 to 50 per cent) is prepared with sterile distilled water. This suspension or cream has been used locally in the treatment of wound infections as an oxidizing anti-bacterial product.

### CATIONIC AGENTS

The germicidal properties of various types of soaps have been investigated by numerous workers. While certain soaps have some anti-bacterial properties, they are not satisfactory germicides against pathogenic organisms found on the skin. They are, however, of value in the mechanical removal of microorganisms.

The discovery of compounds which in solution have a low surface tension and possess detergent, germicidal, keratolytic, and emulsifying actions represent a major advance in skin disinfection technic. These substances are designated as the *cationic detergents*. Solutions of ordinary soaps are *anionic detergents*. Solutions of these two substances are incompatible because concentrations of soap of as low as 0.1 per cent may reduce the germicidal activity of the cationic detergents. Cationic activity is increased as the pH is raised. The cationic detergents are less efficient as germicides in the presence of serum because they combine with protein and organic matter. The cationic detergent anti-infectives inhibit the metabolism and viability of commonly-occurring nonsporulating bacteria. Bacterial spores remain viable even after prolonged contact with these solutions. The cationic detergents are modifications of the general formula:



in which R is an alkyl side chain of varying length and composition.

The cationic surface-active agents are referred to as quaternary germicides. These quaternary salts are readily water-soluble, stable, and nonvolatile in solution, and they are compatible with many acids, alkalies, and salts. These compounds are relatively odorless and colorless, and their toxicity is quite low in the dilutions employed as antiseptics.

Domagk in 1935 studied the germicidal properties of a homologous series of alkyl benzylammonium chlorides. He established the importance of the long alkyl chain and the quaternary nitrogen atom as necessary for antiseptic action.

#### Benzalkonium Chloride, U.S.P. (Zephiran chloride).

This agent is a mixture of alkyl dimethylbenzylammonium chlorides in which R represents a mixture of alkyls from $C_8H_{17}$ to $C_{18}H_{37}$. It is a white, amorphous powder, soluble in water. *Benzalkonium Chloride Solution, U.S.P.*, is a 1:1000 aqueous solution. Zephiran chloride tincture is a 1:1000 alcohol-acetone-aqueous solution. For cleansing a skin area the tincture is generally preferred. The aqueous solution is used in those regions where soap or alcohol would produce irritation.

Benzalkonium chloride is considered in detail as representative of the class of cationic agents. The differences in the group of compounds discussed in this section are minor.

**Toxicity.** Benzalkonium chloride aqueous solution 1:1000 can be given by mouth to guinea pigs as their only source of fluid for months without deleterious effect. Rabbits tolerate 1.2 ml./kg. of a 10 per cent solution subcutaneously or intraperitoneally. A 1:100 solution applied to the shaved skin of rabbits and allowed to dry was found to be safe and caused no irritation. If gauze pads are saturated with a 1:100 solution and held in contact with the skin, a period of 24 hours is the longest exposure time for minimal skin reaction. Quite severe areas of erythema are evoked by longer periods of contact or higher concentrations. Some of the fatty acid salts of the quaternary ammonium compounds appear to be primary irritants or skin sensitizers.

**Therapeutic use of benzalkonium chloride.** The advantages of a clear, colorless, neutral, nonirritating emollient solution of high germicidal potency are obvious. The phenol coefficient measured against *E. typhosa*, *S. aureus*, *S. hemolyticus*, and *S. viridans* is greater than 400 at 37°C. For the preoperative disinfection of the unbroken skin and for superficial injuries and infections, the tincture is recommended. For denuded skin areas and mucous membranes, dilutions of 1:2,000 to 1:10,000 of the aqueous solution are employed. For instillation and irrigation of the eye or vagina, a 1:2000 to 1:5000 aqueous solution is used. For bladder and urethral irrigation, a concentration of not more than 1:20,000 of the aqueous solution is recommended; for retention lavage of the bladder, a concentration of 1:40,000 is used. For wet dressings applied to denuded areas, an aqueous solution of 1:5000 is employed.

Instruments, rubber gloves, etc., may be sterilized and then stored in benzalkonium chloride solution, 1:1000, containing 0.5 per cent sodium nitrite. For disinfecting operating room equipment, a 1:5000 solution is used. It should be stressed that the cationic detergents cannot be substituted for heat sterilization of surgical instruments.

A special feature of the action of the cationic detergents is the prolonged germicidal effect that persists at the site of application, *e.g.*, metal surgical apparatus and operating room equipment. The suppression of odors is a useful action of these solutions.

The cationic antiseptics are not effective against fungi, viruses, or bacterial spores. They are adsorbed on skin surfaces and combine readily with proteins; therefore their activity is reduced in the presence of serum and wound exudates. They are believed to form a film on the skin. The outer surface of this film is anti-bacterial, while the inner side is not. The nature of this protective film in serving as an antiseptic skin bacterial barrier is not understood.

*Roccal* is a 10 per cent solution of benzalkonium chloride (technical) intended for general disinfection purposes. It is not for surgical use. As a general disinfectant in the dairy, baking, meat packing, and food handling industries, one oz. of the 10 per cent solution to 4 gal. of water provides a nontoxic germicidal solution that is satisfactory for the sterilization of utensils, equipment, and food containers.

### Benzethonium Chloride, U.S.P. (Phemerol chloride).

This agent is benzyldimethyl{2-[2-(*p*-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl}ammonium chloride. It is a quaternary ammonium compound belonging to the cationic group of detergents. *Tincture of Phemerol Chloride* 1:500 and *Benzethonium Chloride Solution, U.S.P.*, 1:1000 are proposed as general-purpose germicides and antiseptics. These solutions are used in cleansing wounds, lacerations, and infected skin surfaces.

### Cetylpyridinium Chloride, U.S.P. (Ceepryn chloride).

This is the monohydrate of the quaternary salt of pyridine and cetyl chloride. Tincture of Ceepryn chloride 1:200 or 1:500 is an alcohol-acetone-aqueous solution intended for topical application. An isotonic solution 1:1000 is commercially available. It is made isotonic by the addition of sodium phosphate. For antiseptic purposes for delicate mucous membranes, a 1:5,000 to 1:10,000 dilution is employed. *Cetylpyridinium Chloride Solution, U.S.P.*, is a 1:1000 aqueous solution.

### Methylbenzethonium Chloride, U.S.P. (Diaparene chloride).

This substance is benzyldimethyl{2-[2-(*p*-1,1-3,3-tetramethylbutylcresoxy)-ethoxy]ethyl}ammonium chloride, a quaternary ammonium salt with surface-active and antiseptic properties similar to those of the other cationic detergents. It is not used, however, as a general-purpose local antiseptic. It is employed as an agent in the prevention of ammonia dermatitis in infants by disinfection of diapers. As a residue on the diaper cloth the compound exhibits a bacteriostatic effect against urea-splitting organisms. It appears to have a low systemic toxicity and not to produce sensitizing reactions. Methylbenzethonium chloride may be applied topically as a 0.1 per cent ointment or lotion, or a 0.055 per cent powder.

### Triclobisonium Chloride (Triburon chloride).

Triclobisonium chloride is a bisquaternary ammonium compound. Chemically it is N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-dimethyl-1,6-hexane-diamine bis-(methochloride). Triclobisonium chloride is a topically applied anti-bacterial agent for the management of superficial skin infections and vaginitis. Grunberg and Schnitzer (1959) found triclobisonium to be effective against *Staphylococcus pyogenes* var. *aureus*, including some strains resistant to commonly used antibiotics. The agent is effective against *S. pyogenes*, *D. pneumoniae*, *L. monocytogenes*, and *S. typhii*. Not all strains of *E. coli* are sensitive. Higher concentrations are required to inhibit *P. aeruginosa*, fungi, and *T. vaginalis*.

Triclobisonium has been used with favorable results in impetigo contagiosa, acute folliculitis, furunculosis, infectious eczematoid dermatitis, and secondarily infected dermatoses. A 0.1 per cent ointment or cream is employed. In *T. vaginalis*, monilial, and nonspecific vaginitis a 0.1 per cent suppository is used.

## ANTISEPTIC DYES

Certain organic dyes possess the specific effect of combining with and penetrating living bacterial or tissue cells. The vital dyes, as they are called, have been useful in the classification of microorganisms, *e.g.*, gentian violet in staining gram-positive organisms. These staining properties of the dyes are apparently related to oil-water solubility effects, physicochemical changes, or the hydrogen-ion concentration of the tissue or bacterial cell. The azo dyes and the acridine and rosaniline derivatives are considered in this section. The weak antiseptic properties of these dyes may be related to their affinity for bacterial cells.

### Phenazopyridine (Pyridium).

This azo dye is $\beta$-phenylazo-$\alpha'$-$\alpha'$-diaminopyridine monohydrochloride. It is a brick red, water-soluble, crystalline powder. It has been used in acute and chronic infections of the genitourinary tract in oral doses of 0.2 gm. 1 to 3 times a day, and as a local application by irrigation of a 1 per cent solution. Phenazopyridine is actively antiseptic as it is excreted in the urine. The compound, however, is altered in the body, possibly oxidized to a hydroxy derivative which is practically inert. The urine of patients taking the drug by mouth acquires an orange-red to dark red color if acidified. A local anesthetic effect is observed clinically when a 1 per cent phenazopyridine solution is employed by instillation into the bladder via the urethra.

The local anesthetic action of phenazopyridine appears to be its major contribution in genitourinary infections. It is used mainly to afford relief of discomfort in cystitis while other remedies are being instituted to remove the cause of the pain.

### Methylrosaniline Chloride, U.S.P.

This dye, which is also designated as *gentian violet medicinal*, *methyl violet*, or *crystal violet*, is hexamethylpararosaniline chloride, usually admixed with pentamethylpararosaniline chloride and tetramethylpararosaniline chloride. It is a dark green powder having a metallic luster. It is soluble in water. Solutions of this dye have been used as an antiseptic in wounds and on mucous membranes. Their use in this manner, however, appears to have little place in modern medical practice. The rosaniline dyes may have virtue in the treatment of superficial fungus infections of the skin. A solution of 1:100 to 1:1000 is employed for this purpose. Gentian violet is also used as an anthelmintic (see page 189).

## MISCELLANEOUS ANTI-INFECTIVES

In recent years a number of nitrofuran antimicrobial agents have been discovered. The first was nitrofurazone, used topically as a wide-spectrum anti-bacterial substance. Nitrofurantoin is used in genitourinary tract infections. Other related compounds are reported to be bacteriostatic or bactericidal and fungicidal, and still others are chemotherapeutic for bacterial enteritis and dysentery.

These drugs apparently have a specific and unique mode of action on microbial enzyme systems. While their mechanism of action is not known, they do inhibit a step in carbohydrate catabolism before the Krebs cycle in the formation of coenzyme A. The sulfonamides and a number of antibiotics are known to be anti-bacterial through other mechanisms. For this reason there may not be bacterial cross-resistance.

Unfortunately a number of persons are very sensitive to the nitrofuran derivatives and develop urticarial rash after contact with these drugs. A few patients have developed hemolytic reactions. The hemolytic anemia produced by nitrofurantoin appears to be limited to those individuals who have inherited a peculiar defect of the erythrocyte. This is an intrinsic abnormality similar to that observed in persons susceptible to the hemolytic action of primaquine, sulfanilamide, and acetanilid (see page 760). The defect can be recognized by demonstrating that the concentration of reduced glutathione in the red cells decreases when the patient's blood is incubated with acetylphenylhydrazine. The reduced glutathione level of normal erythrocytes does not change in this test. It is possible that a number of the reported hemolytic reactions to many drugs may have as their basis this unusual inherited erythrocyte abnormality.

A systematic study of the transport of antimicrobial agents through the interstitial fluid has not been made, even though the interstitial spaces are frequently the loci of microbial infections. It is of interest that Buzard *et al.* (1961) found that the extent of plasma binding determined the apparent rate of transfer of a group of nitrofuran drugs to the lymph. Unbound nitrofurantoin entered the lymphatic circulation following oral doses as determined by the plasma: lymph ratio in dogs.

### Nitrofurazone, N.F. (Furacin).

This drug is 5-nitro-2-furaldehyde semicarbazone. Nitrofurazone is a lemon yellow, odorless, crystalline powder. It is soluble in water to the extent of 1 in 4200. In solution the compound possesses bacteriostatic and bactericidal properties. In dilutions of 1:200,000 to 1:300,000 it is inhibitory to bacterial growth and is bactericidal at 1:50,000 to 1:75,000 dilutions *in vitro.*

Nitrofurazone in the form of *Nitrofurazone Soluble Dressing, N.F.*, is a 0.2 per cent concentration in a water-soluble, ointment-like base. It is used for topical application in the prophylaxis and treatment of superficial mixed infections common to contaminated wounds, burns, ulcerations, and certain skin diseases. The soluble dressing has been used as an adjunct to surgery in skin grafting and in the treatment of osteomyelitis. Many individuals are sensitive to local applications of the compound, and skin reactions frequently have been observed following its use. Organisms resistant to the sulfonamides, penicillin, or streptomycin may be susceptible to nitrofurazone.

**Nitrofurazone Solution, N.F.,** is a light yellow, somewhat viscous liquid containing 0.2 per cent nitrofurazone in a polyethylene glycol solvent mixture. The solution is instilled into the external meatus in the control of purulent otitis.

### Nitrofurantoin, U.S.P. (Furadantin).

This drug is a furan derivative related to nitrofurazone. It is N-(5-nitro-2-furfurylidene)-1-aminohydantoin. This substance is effective against bacteria causing urinary tract infections including many strains of *Proteus*, *Aerobacter*, and *Pseudomonas* species. It is a yellow, crystalline compound, soluble in water to the extent of 18 mg./100 ml. at pH 7. It is said not to give rise to crystalluria when administered orally in therapeutic doses.

Nitrofurantoin has a low oral toxicity. It is administered orally in the treatment of chronic urinary tract infections in daily doses of 5 to 8 mg./kg. It has been used with some success in patients with urinary tract infections that had failed to respond to other anti-bacterial agents. *Proteus* and *Pseudomonas* species infections may require a maximum dose of 10 mg./kg.

**Nitrofurantoin Oral Suspension, U.S.P.,** is a 0.5 per cent suspension. Available tablets contain 50 or 100 mg. of the drug.

Nitrofurantoin occasionally has caused a diffuse, erythematous, maculopapular eruption of the skin. Oral doses may produce gastrointestinal symptoms, with nausea and emesis. Peripheral neuropathy has been reported following prolonged high dosage, and in one case the effects were persistent (Uesu, 1962). In the presence of anuria, oliguria, or severe renal damage the drug is contraindicated.

### Boric Acid, U.S.P.

Boric acid ($H_3BO_3$) is a colorless, odorless, crystalline compound or white powder. It is slightly unctuous to the touch. It is soluble in water to the extent of 1 gm. in 18 ml. Boric acid has been used in medicine for many years as a mild antiseptic dusting powder. It is not a disinfectant, and its solutions are of low antiseptic value. In recent years, as a result of accidental ingestion and poisoning with boric acid, it has been suggested that this compound be deleted from medical practice entirely.

A saturated (4 per cent) aqueous solution is used as a collyrium. It is useful as a weak acid solution in cases of accidental contamination of the eyes by an alkaline fluid. Because boric acid is such a weak antiseptic, the Food and Drug Administration regulations require that ophthalmic solutions containing boric acid be sterilized by boiling in water and stored in sterile containers.

**Toxicity of boric acid and borax.** Boric acid and sodium borate (sodium tetraborate, borax)

have the same fate in the animal body. Doses of 5 gm. or larger by mouth are acutely toxic. Boric acid has produced renal injury, and death has resulted from its oral ingestion. The symptoms are nausea and vomiting with abdominal pain, diarrhea, weakness, and collapse. Secondary effects include dyspnea, muscular debility, scarlatinal eruptions, fall in body temperature, cardiac irregularities, and death from renal failure. The treatment is symptomatic.

Although boric acid is concentrated in the central nervous system in poisoning, the mechanism causing the convulsive tremors, lethargy and coma is unknown. Ling and associates (1957) found boric acid produced only a negligible depression of oxygen uptake in rat cerebral tissue with pyruvate or glucose substrate. In addition, boric acid did not appear to act preferentially on cerebrum, cerebellum, medulla oblongata, or hypothalamus-thalamus tissue.

Deaths have been reported following the use of boric acid dusting powders on infants (Goldbloom and Goldbloom, 1953). Other workers have shown that boric acid can be absorbed through the skin of rabbits, especially if the skin is injured. Solutions of boric acid in urine appear to be more readily absorbed. These observations have raised the question of the desirability of using boric acid dusting powder on infants. Fisher (1955) made periodic analyses of the blood of a large number of infants treated with a commercial 5 per cent boric acid dusting powder for 1 year. They did not find any significant increase in the blood level of boron during this period. Subsequently, Freimuth and Fisher (1958) found that whereas boric acid and borax were readily absorbed from the skin of rabbits when applied in 5 per cent and 8 per cent solutions, respectively, calcium metaborate and boric acid in the presence of talc were poorly absorbed. This they attribute to the insolubility of calcium metaborate. An increase in pH to 9 results in decreased absorption of boric acid from aqueous solution, which may explain the influence of talc on the absorption of boric acid from the skin.

There is wide divergence of opinion regarding the merits of boric acid in medical practice. Some hospitals have prohibited its use, while some dermatologists insist that the drug is useful and should be retained for the physician's choice. The wide publicity given in recent years to the dangers of boric acid accidental poisoning should alert physicians, hospital attendants, and the mothers of small children to the hazards associated with its use.

## ANTIFUNGAL AGENTS

The principal skin diseases encountered which are clinically attributable to fungi are the dermatophytoses caused by *Trichophyton mentagrophytes*, *T. rubrum*, and *Epidermophyton floccosum* and related organisms. In addition, ringworm infection in children caused by *Microsporum lanosum* and *M. audouini* should be mentioned. The *M. audouini* is especially resistant to antifungal agents. Other types of superficial lesions or mucous membrane involvement may be caused by *Candida albicans* and other pathogenic yeasts. These are annoying, persisting infections, not usually sufficiently grave to require hospitalization, yet potentially dangerous.

The fungi causing infections in internal organs, the *deep mycoses*, are less commonly encountered in medical practice. The recognition of these mycoses is important because most of them produce diseases which have a high mortality. Specific therapy is available for some of these mycotic infections, *e.g.*, sulfadiazine in actinomycosis, and reference is made to these compounds in the sections dealing with these drugs. The unusual persistence of the cultural and biochemical characteristics of certain fungi of human origin has been reviewed by Castellani (1962). Some fungi that were subcultured for 50 years did not change their growth patterns; others changed permanently and irreversibly, and still others followed a cyclical pattern through the years.

The discovery of the antifungal properties of the long chain fatty acids *in vitro* opened a new era in therapy of skin mycotic infections. Sodium propionate and sodium undecylenate were found to be useful in clearing superficial mycoses and common fungus skin infections. In 1946 salicylanilide, long used as a fungicide in textiles, was introduced in treating ringworm of the scalp. However, no completely satisfactory antifungal therapy was available until 1959, when the effectiveness of the antibiotic griseofulvin was demonstrated.

Of the many substances tried as antimycotic or antifungal agents, none was satisfactory for topical use, and generally they were too toxic for systemic therapy. While these agents would demonstrate potency in laboratory tests *in vitro*, they were disappointing when used in treating fungus infections in man. It is now suspected as a result of the discovery of griseofulvin that topically applied drugs are not able to penetrate the keratin layer of the skin, hair, or nail to reach the site of the offending fungus. A drug like griseofulvin, administered systemically, seems to endow the cells eventually destined to produce keratin with fungi-resisting properties. This antifungal effect persists as the cells become keratinized. It has been clearly demonstrated that griseofulvin is deposited within the skin cells and hair shafts, suggesting that there is some form of circulation within the keratin of the epidermis. The successful use of griseofulvin in dermatophytic infections appears to be related to its incorporation in some manner in keratinized tissue.

The antibiotics that exhibit antifungal properties are discussed on page 120.

### Undecylenic Acid, N.F. (Desenex).

This yellow liquid has a characteristic odor. The structure is closely related to the other members of the series of antifungal agents that will be described.

$H_2C{=}CH(CH_2)_8COOH$

Undecylenic Acid, N.F.

Undecylenic acid is a potent fungistatic agent used in the treatment of superficial fungus infections. It is applied topically in the form of a 10 per cent alcoholic solution. If local application is followed by irritation, the solution may be diluted with 9 parts of water to provide an opalescent suspension that is less irritating.

**Compound Undecylenic Acid Ointment, N.F.,** is a 5 per cent undecylenic acid, 20 per cent zinc undecylenate ointment in a washable ointment base. This preparation is used in treating dermatomycosis pedis, referred to as "athlete's foot."

A combination of 2 per cent undecylenic acid, 25 per cent zinc undecylenate, and 5 per cent salicylanilide is employed in the treatment of *tinea capitis* infections. Sodium caprylate is also employed topically as a 20 per cent solution in the treatment of superficial fungus infections of the skin.

### Salicylanilide, N.F. (Ansadol, Salinidol).

This antifungal agent is used externally in the treatment of tinea capitis caused by *Microsporum audouini*. It is generally applied as a 5 per cent ointment with other fungistatic agents.

### Hexetidine (Sterisil).

Hexetidine is 5-amino-1,3-bis-(β-ethylhexyl)-5-methylhexahydropyrimidine. This substance is incorporated in a vaginal gel for the treatment of *Trichomonas vaginalis* and *Hemophilus vaginalis* infections. The preparation, containing 0.1 per cent of hexetidine, is claimed to be effective in trichomonal, monilial, or "nonspecific" vaginitis.

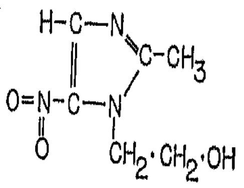
Hexetidine contains a pyrimidine nucleus similar to that of thiamine. It is suspected that bacteria incorporate the foreign molecule in their metabolic pool and that energy utilization is blocked as a result. This compound exhibits anti-bacterial properties against many gram-positive staphylococci and streptococci and gram-negative bacilli, in addition to its antifungal activity.

## VAGINAL TRICHOMONIASIS

### Metronidazole (Flagyl).

The *Trichomonas* organism is a flagellate protozoa belonging to the class *Mastigophora*. Vaginal trichomoniasis is a troublesome, persistent disease thought to be an important etiologic factor in leukorrhea. The infection is a serious deterrent to the physical and emotional comfort of many women.

Metronidazole is a specific drug for the treatment of vaginal trichomoniasis. It is 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole. The substance is a pale yellow, crystalline powder, slightly soluble in water.



Metronidazole, Flagyl

Metronidazole is readily absorbed from the gastrointestinal tract, and the drug is prescribed for systemic therapy. It is also employed in the form of vaginal inserts to supplement the effects of systemic medication.

The trichomonacidal activity of metronidazole was determined *in vitro* in standardized cultures of *T. vaginalis*. The minimal concentration that destroyed 99 per cent of the organisms in 24 hours was 1:400,000. This effectiveness *in vitro* far exceeded that of other known compounds. Subsequently, *in vivo* activity was demonstrated in animals. Urinary excretion studies in rats indicated that approximately ⅙ of an orally administered dose is excreted in the urine in 2 to 5 days. The drug did not produce significant toxic effects in several species of animals; therefore it was administered to patients. Early observations on the efficacy of metronidazole in the treatment of trichomoniasis were reported in France in 1959. In the United States the results reported to date have been favorable.

Metronidazole is indicated in the treatment of trichomoniasis in both male and female patients when the organism has been demonstrated by wet smear or culture, and for the sexual partners of these patients who have a recurrence of the infection, when a trichomonal infection is demonstrated in the urogenital tract of the sexual partner. The drug is specific for *T. vaginalis*, and it should not be employed in the treatment of other conditions.

The dosage in women is one 250-mg. tablet orally 3 times daily for 10 days. Repeated courses of the drug may be required but are not recommended until an interval of 4 to 6 weeks has elapsed. Leukocyte counts should be made before, during, and after treatment. Vaginal inserts of 500 mg. are used daily in addition to the oral dosage, which is then reduced to 2 tablets daily for 10 days. Topical vaginal treatment may be indicated in cases of especially stubborn infections.

In men the drug is prescribed only when trichomonads are demonstrated in the urogenital tract. The dose is one 250-mg. tablet 2 times daily for 10 days. When prescribed for the male in conjunction with the treatment of his female partner, the drug should be taken by both patients over the same 10-day period.

Side effects following metronidazole administration are nausea, headache, anorexia, occasional vomiting, diarrhea, epigastric distress, and abdominal cramping. Constipation has also been reported. Some investigators have observed a browning of the tongue, and patients have reported a metallic, unpleasant taste. A depression of the white blood cell count has occurred, but these values promptly returned to normal after discontinuance of the therapy. Conservative use of the drug includes a leukocyte count at proper intervals.

Dizziness, vertigo, and, very rarely, incoordination and ataxia have been reported. Although the drug does not influence the blood-forming elements and has no effect on blood, it should not be administered to patients with a blood dyscrasia or a history of this disease because the nitroimidazole chemical structure suggests possible untoward hematologic effects. Patients with a disease of the central nervous system should not receive the drug. At the present time it is recommended that metronidazole not be administered during pregnancy.

The use of metronidazole may encourage the growth of *Candida* organisms, and symptoms of moniliasis may be increased after cure of trichomoniasis.

The numerous reports of the effectiveness of this drug in the therapy of a difficult medical problem suggests that a significant contribution to chemotherapy has been achieved in the discovery of metronidazole.

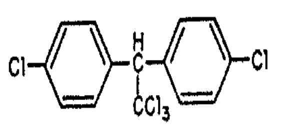
## ANTIPEDICULAR AGENTS

Antipedicular agents are employed in the treatment of louse infestations. Lice infesting the scalp are the species *Pediculus humanus* var. *capitis*. Infestation of the skin of the body is recognized as *P. humanus* var. *corporis*. Infestation of the pubic hair with *Phthirus pubis*, the crab louse, may also extend to the axillas, eyebrows, and eyelashes. The disease condition is characterized by an intense and overpowering itching and by cutaneous lesions. The antipedicular agents are also used in the treatment of scabies, which is a contagious disorder of the skin caused by the mite *Sarcoptes scabiei*. The burrowing beneath the skin by the female mite causes itching and severe irritation.

A number of effective agents have been developed for the treatment of scabies and pediculosis. These drugs have improved the therapy of these distressing skin diseases. The substances that are most useful are chlorophenothane (DDT) hexachlorocyclohexane, benzyl benzoate, isobornyl thiocyanoacetate, pyrethrum, and crotamiton.

### Chlorophenothane, U.S.P. (DDT).

This agent is 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane. In addition to the insecticidal properties of DDT, the compound is efficacious in the treatment of pediculosis and scabies. A 10 per cent dust is employed.



Chlorophenothane, U.S.P.
DDT

### Benzyl benzoate chlorophenothane ethylaminobenzoate (Enbin).

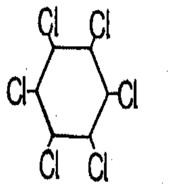
This is an oil-in-water emulsion of 11.3 per cent benzyl benzoate and 1 per cent DDT, and 2 per cent ethylaminobenzoate. Benzyl benzoate and DDT are effective scabicides; 2 per cent ethyl aminobenzoate is added as an ovicide and for its local anesthetic properties.

Treatment consists of applying an emulsion of this product by rubbing and allowing the preparation to remain in contact with the affected areas for 24 to 48 hours. One application is usually sufficient to control either pediculosis or scabies. Care must be exercised to avoid contact with the eyes or mucous membranes. Temporary smarting of tender areas of the skin may occur. Repeated applications should be avoided. When this preparation has been employed in the treatment of scabies, the treatment time has been greatly reduced as compared with older forms of therapy.

**Benzyl Benzoate Lotion, N.F.,** and **Saponated Benzyl Benzoate, N.F.,** are widely used as scabicides.

### Gamma Benzene Hexachloride, U.S.P. (Gammexane, Lindane).

Benzene hexachloride, hexachlorocyclohexane, consists of 4 isomers—alpha, beta, gamma, and delta. The gamma isomer possesses the greatest insecticidal activity.



Gamma Benzene Hexachloride, U.S.P.

This product is a white solid, insoluble in water. It is more effective in lower concentrations as an insecticide than DDT and usually kills insects very quickly. A 1 per cent ointment of gamma benzene hexachloride is effective in the treatment of scabies. Complete relief from pruritis is provided within 24 to 48 hours in most patients. One application of the compound in a vanishing cream base without preliminary bathing is usually sufficient. Commercial preparations containing 1 per cent gamma benzene hexachloride are *Kwell* and *Gexane*.

Gamma benzene hexachloride, like DDT, is potentially a toxic substance, especially if ingested. Fortunately, single applications are usually sufficient in scabies, so that the danger of systemic absorption and toxicity is not great. When applied properly in a 1 per cent concentration after bathing, left on the skin for 24 hours, and then removed with another thorough bath, the substance is not irritating.

### Isobornyl thiocyanoacetate (Bornate).

This substance, in the form of an impure mixture with dioctyl sodium sulfosuccinate as a mineral oil emulsion, is effective in treating pediculosis. A 5 per cent isobornyl thiocyanoacetate concentration is used. It is applied externally to the hairy surfaces of the body, worked into a lather, and allowed to remain in contact with the area for 10 minutes. The treated surface is then washed thoroughly. The emulsion must not be permitted to remain in contact with the skin too long, because it is a skin irritant. Care must be exercised to avoid contact with the eyes or mucous membranes.

### Crotamiton (Eurax).

This antipedicular agent is ethyl-*o*-crotonotoluide, used in the treatment of scabies. The agent is applied topically as a 10 per cent cream or a lotion. Sensitivity reactions have rarely been encountered following its use. If acute vesicular dermatitis is present, the preparation should not be used. At the present time many dermatologists consider this agent the drug of choice in scabies.

### Toxicity of the scabicides and pediculicides.

The high potency of these agents and their selective action make them very satisfactory therapeutic agents. They are toxic, however, when applied improperly, and some individuals may exhibit an idiosyncrasy to these substances. If ingested, they are poisonous. Because the chlorinated hydrocarbon compounds are most widely used as insecticides as well as for therapeutic purposes, a more complete description of their toxicology will be presented.

**Toxicology of chlorinated hydrocarbon insecticides.** DDT and hexachlorocyclohexane are used in the control of human lice. DDT is probably the most widely used insecticide, and toxicologically it assumes the greatest importance among the chlorinated hydrocarbon insecticides. In table 16-1 a list of these insecticides is given. These agents are considered as a group, but their mode of action is not known, and it is possible that their similar toxic effects may reflect different mechanisms of action. The Communicable Disease Center of the U. S. Public Health Service has reported detailed information on the toxicity of these insecticides and other economic poisons. The toxicity data presented here are taken from this report. Only a summary of the character of poisoning with DDT and hexachlorocyclohexane is presented. In general, the characteristic symptoms are typical of the group. The solvent in which the compound is exhibited may contribute to the toxic syndrome, either through its inherent toxicity or by solubilizing the insecticide. Thus the symptoms of poisoning may be referable to the solvent alone or may be characteristic of the active ingredient.

*DDT poisoning.* DDT is absorbed from the intestinal tract and from the lungs. It is not absorbed through the skin as a dry dusting powder. Solutions or emulsions of DDT are absorbable through the skin and constitute a hazard. Oils and fats promote the absorption of DDT from the gastrointestinal tract. A single ingestion of 10 mg./kg. produces toxic effects in some, but not all individuals. Subjects made ill by this dose have not shown convulsions. When the dosage level was 16 mg./kg. or greater, convulsions frequently occurred. A dose as high as 285 mg./kg. has been taken orally without fatal results. Vomiting usually follows even small doses of DDT, so that the amount retained is not determinable.

In acute poisoning the time of onset of symptoms may be delayed from 30 minutes to 2 to 3 hours or longer. There is paresthesia of the tongue, lips, and part of the face. In more severe poisoning the paresthesia may extend to the extremities. The subject suffers from a sense of apprehension, a disturbance of equilibrium, dizziness, confusion, and a characteristic tremor. Convulsions may intervene in severe poisoning. The pulse is irregular or abnormally slowed. Blood pressure and temperature remain essentially normal. Except in the most severe cases recovery is well advanced or complete in 24 hours. There is no well-described fatal case of DDT poisoning that is not complicated by other poisons and the solvent, although a number of fatalities have followed the ingestion of DDT solutions. In these cases the poisoning has frequently been characteristic of the solvent.

TABLE 16-1

*Chlorinated Hydrocarbon Insecticides**

Chlordane: 1,2,4,5,6,7,8,8-octachloro-3α,4,7,7α-tetrahydro-4,7-methanoindane
Hexachlorocyclohexane, benzene hexachloride: Lindane is the pure gamma isomer
Chlorophenothane, DDT: 2,2,bis-(*p*-chlorophenyl)-1,1,1-trichlorethane
Dieldrin, Octalox: 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4α,5,6,7,8,8α-octahydro-1,4-endo, exo-5,8-dimethanonaphthalene
Dilan: mixture of nitrobis-*p*-chlorophenyl propane and nitrobis-*p*-chlorophenyl butane
Heptachlor: 1,4,5,6,7,8,8 heptachlor-3α,4,7,7α-tetrahydro-4,7-methanoindane
Toxaphene: an impure chlorinated camphene

* Many commercial grades are impure mixtures of chemically related compounds.

Chronic DDT poisoning presents a difficult problem. In a study of 51 human volunteers, 18 ate 35 mg. of DDT per man per day (0.5 mg. per kg. per day) for as long as 18 months without producing any adverse effect. A dosage of 0.5 mg./kg. per day is about 200 times the daily rate at which the average citizen in the United States receives DDT in his diet. At the higher dose level a tissue equilibrium was reached. It is estimated that the concentration of DDT in prepared meals is in the order of 0.25 ppm. (dry basis) and is equivalent to a dosage of 0.0026 mg./kg./day (Walker *et al.*, 1954). In a similar experiment with control groups and groups receiving 3.5 and 35 mg. per man per day, the total of 51 experimental subjects remained symptom-free and showed no evidence of illness related to exposure to DDT (Hayes *et al.*, 1958).

Careful examinations of workers exposed extensively to DDT for as long as 6.5 years revealed no abnormalities which could be attributed to the insecticide (Ortelee, 1958).

According to Hayes and associates (1958), there has been no significant increase in the storage of DDT in the fat tissues of the general population of the United States since 1950. There is strong evidence that stored DDT and its metabolite DDE[2,2 bis-(*p*-chlorophenyl)-1,1-dichloroethylene] in persons without occupational exposure to these compounds results from the presence of these insecticidal residues in dietary fats of animal origin.

The findings of Dale *et al.* (1962) support the observations that most of the DDT stored in the body is in neutral fat. When this fat is used up during starvation, the concentration of DDT and DDE in the remaining adipose tissue is increased. They conclude that DDT does not present a hazard to people subject to starvation. This matter is of considerable public health interest because DDT and related compounds are employed so extensively in agriculture. Walker and associates (1954) found that all meals which they analyzed contained small but measurable amounts of DDT or DDE. It is of interest that the major portion of DDT intestinally absorbed in the rat and goat can be recovered in the chyle. If this pattern of distribution holds for man, only relatively low amounts of DDT will be recovered in the urine until tissue equilibrium has been established (Rothe *et al.*, 1957).

A recent monograph edited by Muller (1959) reviews the entire subject.

*Hexachlorocyclohexane poisoning.* The various isomers of hexachlorocyclohexane have different actions. The gamma and alpha isomers are central nervous system stimulants and produce convulsions. The beta and delta isomers are depressants of the central nervous system. Lindane, the gamma isomer, has produced convulsions in man following a 45-mg. dose as a vermifuge. Larger doses in some individuals have been given without apparent harmful effect. Poisoning in children has resulted from eating tablets of Lindane intended for use in insecticide thermal vaporizers.

The symptoms of poisoning resemble those produced by other chlorinated hydrocarbons. They are excitement, hyperirritability, loss of equilibrium, clonic-tonic convulsions, and later depression. There is evidence that the pulmonary edema and vascular collapse that may occur is of neurogenic origin. Lindane may produce allergic manifestations after a period of sensitization.

*Treatment of poisoning with the chlorinated hydrocarbons.* Attention should be directed to sedation of the patient and removal of the poison if it has been taken internally. Gastric lavage and saline laxatives may be used. Skin contamination is removed with soap and water. Pentobarbital and phenobarbital are the sedatives of choice. A dose adequate to sedate without inducing sleep is desirable. In the presence of hyperexcitability or convulsions, these doses may be relatively large. Calcium gluconate given intravenously may be helpful in controlling the convulsions. Epinephrine is contraindicated because this agent may induce ventricular fibrillation in the presence of poisoning by chlorinated hydrocarbons.

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# 17

# The Pharmacologic Response of the Sensory Nerve Endings to Local Anesthetics

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### An Introduction to the Local Anesthetics

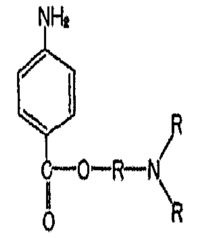
The local anesthetics can be divided into essentially two classes. The first class is made up of those which cause local anesthesia through the production of cold; these are liquids of low boiling points such as ether, ethyl chloride, methyl chloride, and "$CO_2$ snow." The second class is made up of those which have a specific effect on the sensory nerves or their endings; to this class belong cocaine and the numerous synthetic anesthetics. A third group, the protoplasmic poisons, might be included in this classification of local anesthetics. However, the mechanism of action of these latter substances differs from that of the commonly used local anesthetic drugs, and the principal member of this class, quinine and urea hydrochloride, is discussed on page 157. The injection of ethyl alcohol into a nerve trunk to afford relief from pain is described on page 280. The antihistaminic agents are local anesthetics,

and this property is an attribute in their clinical use. These drugs are described in Chapter 58.

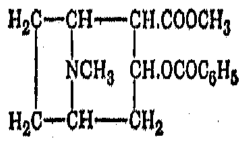
In this chapter cocaine and procaine will be considered first because of their historic role. In addition, among the large number of synthetic local anesthetic drugs, procaine, after 60 years, holds a unique place in medical practice. In table 17-1 the local anesthetics recognized in the *United States Pharmacopeia*, *National Formulary*, and *New and Nonofficial Drugs* are tabulated in alphabetical order. These are discussed briefly in the succeeding section.

Throughout the discussion that follows, reference will be made to the use of local anesthetics in *infiltration anesthesia*, *nerve block anesthesia*, and superficial or *topical anesthesia*. Consideration is given to the use of local anesthetics in *spinal* and *extradural* anesthesia in Chapter 22.

The synthesis of the large group of local anesthetics has to a great degree resulted from the effort to prepare simple cocaine derivatives devoid of habit-forming properties and lower in toxicity. Those anesthetics related to cocaine chemically are esters of *p*-aminobenzoic acid in which an alkyl amine has been introduced into the alkyl group thus:



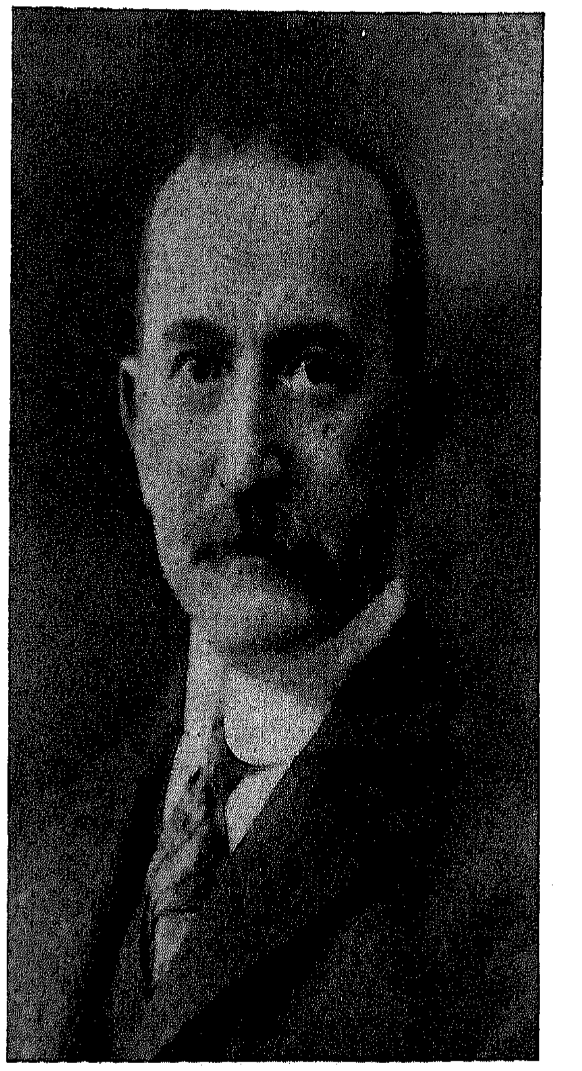
in which R represents different alkyl groups and can be varied in many ways to produce new compounds. The relationship of this basic structure to cocaine can be observed by comparison of the formulas.



Cocaine, N.F.

### Discovery of cocaine.

Many centuries before Pizarro and the Spaniards conquered Peru in the sixteenth century, the aboriginal Indian had discovered that when the leaves of the coca plant were chewed, an insensibility to fatigue resulted. The plant was introduced into Europe as a botanical curiosity. In 1860 Niemann isolated the alkaloid cocaine from the leaves of this plant, *Erythroxylon coca*. Its local anesthetic effect when placed upon the tongue was observed, but it was not until 1884 that Koller first used cocaine in surgery of the eye. This application represented the beginning of the development of local anesthetic drugs in medical practice. The use of cocaine as a topically applied, pain-relieving drug promptly became widespread. As the use of this drug rapidly grew, two serious disadvantages became apparent. Cocaine is quite toxic, and it is habit-forming.



CARL KOLLER
1857–1944
*Astute Viennese surgeon whose observations led to the use of cocaine as a local anesthetic*

Sigmund Freud stated, "Koller can be rightfully considered the discoverer of local anesthesia with cocaine, which has been so important in minor surgery."

Years of investigation elucidated the chemical structure of the compound, and it was finally synthesized by Willstätter is 1902.

The introduction of cocaine into medical practice by Koller is one of the most interesting phases of medical history. In Vienna, in the eighteen eighties, a friend of Sigmund Freud became addicted to morphine. Freud was his physician, and he had tried in vain to arrest the addiction. In 1884 Freud obtained a sample of cocaine from

Merck. He tried it on his patient, hoping to cure him of the opium habit. Concerning this event Sigmund Freud wrote: "In 1884 an important matter, though one which lay outside of my main interests, led me to send to Merck for a supply of the still little-known alkaloid cocaine that I might study its physiological effects." Freud, in conjunction with the surgeon Josef Breuer, made a study of the properties of cocaine. They confirmed what Frederick Wöhler had observed, namely, that "cocaine was a substance which had a somewhat bitter taste and exerted a numbing influence on the gustatory nerves, so that they became almost completely insensitive." Carl Koller was a witness to these experiments. It occurred to Koller to try the effects of cocaine on the sensory nerve endings of the conjunctiva and cornea. Koller used the drug in the eyes of frogs and guinea pigs, then in his own eyes and in those of several of his colleagues. He observed the potent local anesthetic action of the alkaloid. On September 15, 1884, Koller read a paper on the anesthetic action of cocaine at Heidelberg, and a month later, before the Vienna Medical Society. Freud stated: "Koller can be rightfully considered the discoverer of local anesthesia with cocaine, which has been so important in minor surgery."

Halsted (1885) demonstrated that cocaine could be used to produce a nerve block. The work of Halsted in America became the basis for nerve block anesthesia in surgery. In 1885 Corning produced spinal anesthesia in dogs with cocaine, but the clinical application of spinal anesthesia did not occur until the turn of the century. The history of the introduction of cocaine into therapeutics has been given by de Jong and Wagman (1963).

### Methods of evaluating local anesthetics.

The quantitative determination of the degree of local anesthesia produced by various new synthetic compounds is a pharmacologic problem. There are 5 principal methods generally used for the biologic evaluation of these drugs. They are:

1. Anesthesia of the cornea
2. Anesthetic action on mucous membrane
3. Paralysis of nerve endings on direct application
4. Sciatic nerve or lumbar plexus block
5. Human intradermal wheal

In addition to exhibiting local anesthetic activity, the drug must be sufficiently nontoxic to be employed clinically in man in the concentration found to be effective.

Surface anesthesia may be evaluated, employing the web foot of the frog or the mucous membranes of the tongue or oral cavity of man. Subcutaneous or infiltration anesthesia has been measured by the human skin wheal method. A number of studies of local anesthetics have been made, designed to evaluate these drugs clinically.

### Mechanism of action of local anesthetic agents.

Local anesthetic agents will prevent the passage of the nerve impulse at:

1. Sensory nerve endings
2. Ganglionic synapses
3. Neuromuscular junctions
4. Nerve trunks

The blocking of the reflex arc at sensory nerve endings can be readily demonstrated. The strychninized frog shows tetanic seizures when stimuli reach the cord over the posterior roots. If the animal is first immersed in a solution of cocaine hydrochloride and the anesthetic is allowed to affect the skin sensory nerve endings, external stimuli will no longer reach the cord, and the hyperreflexia and convulsions do not appear upon the injection of strychnine. The reflex arc is blocked at the sensory nerve endings in the skin.

The second activity of local anesthetics, *i.e.*, at the ganglionic synapse, can be demonstrated as follows: if the solution perfusing a nerve ganglion contains procaine hydrochloride and stimuli applied to the preganglionic fibers, the postganglionic fibers fail to exhibit stimulation effects. The ganglion is blocked. The neurotransmitter which is responsible for the transmission of the nerve impulse from the pre- to the postganglionic fibers is antagonized by the presence of procaine.

The third response elicited by local anesthetics can be demonstrated by their effect at the neuromuscular junction in striated muscle. Procaine will block the response of acetylcholine in stimulating the contraction of skeletal muscle. In this respect procaine shows an action similar to that of curare. Indeed, the effects of curare and procaine at the neuromuscular junction are additive.

The fourth site of activity of local anesthetics involves the phenomenon of *nerve block* by the direct application of the agent to the nerve trunk or its injection into the surrounding tissue. The agent influences the nerve cells by contact with the plasmic membrane and cytoplasm. Small nerve fibers, which exhibit the greatest surface per unit of volume, are affected before the larger fibers. If cocaine is applied to the vagus nerve, the efferent cardiac-inhibitory fibers, which are smaller, are blocked first. The larger fibers, which are involved in carrying afferent respiratory impulses, are affected less rapidly.

It is apparent from a consideration of the foregoing experiments that local anesthetics manifest a selectivity for nerve structures. Furthermore, these agents interfere with nerve conduction in small concentrations. Their action is reversible. The mechanism of the action of local anesthetics in producing a discontinuity of the capacity of a nerve to transmit an impulse is not clearly understood. Certain cogent data derived from the experiments of many workers in this field do, however, shed light upon the problem. The physiologic mechanisms of peripheral nerve block by local anesthetics have been reviewed by de Jong and Wagman (1963).

Investigators have exposed single nerve fibers to the action of local anesthetics. When cocaine hydrochloride, dissolved in Ringer's solution in a concentration slightly greater than minimal, was applied on Ranvier's nodes, a cessation of the conducting power of the nerve occurred in 0.25 second. In the region between the nodes the cocaine exhibited no effect. It appears, therefore, that the myelin sheath is relatively impermeable to the local anesthetic. Furthermore, the immediate character of the response at Ranvier's nodes suggests that the plasmic membrane contains the target molecules.

Experimentally it has been shown that narcotics (chloroform) and local anesthetics (lidocaine) in low concentrations will disturb an ergosterol film which is fixed at the phase boundary between paraffin oil (lipoid) and water. An almost instantaneous increase in surface tension will result. The view has been expressed that the narcotic drugs produce their effect at surface boundaries by van der Waals' forces exerted between the narcotic and the lipoid phase. The typical local anesthetic type of molecule is "dualistic," exhibiting *lipophilic* and *hydrophilic* properties. The hydrophilic factor in the molecule of a local anesthetic is almost invariably an amino group. This is believed to be attracted to polar groups in the lipoprotein film constituting the plasmic membrane where metallo-ions are present, which are presumably responsible for nerve conduction. The lipophilic portion of the molecule is anchored simultaneously in the lipoid phase of the membrane. This disturbs the nice phase boundary equilibrium and nullifies nerve conduction.

Indeed, the effect of local anesthetic agents on nerve metabolism was studied comprehensively by Watts (1949). Using brain homogenates, this investigator showed that cocaine, procaine, piperocaine, butacaine, tetracaine, and dibucaine inhibit the oxidation of glucose, succinate, and ascorbate. These agents do not, however, affect the anaerobic glycolysis of glucose. Local anesthetics were found to inhibit the oxidation and reduction of cytochrome C. This work on cellular metabolism, coupled with the foregoing adsorption phenomena, provides a tentative hypothesis for the action of these substances.

**Action of local anesthetics as free bases and salts.** It is believed that the local anesthetic drugs act upon the sensory nerve cells as the free base. The water-soluble salts are generally employed, but the oil-soluble base is the active form of the molecule. The addition of alkali salts, such as sodium bicarbonate, to a solution of a local anesthetic increases its potency. It is generally presumed that the body fluids perform this buffer role *in vivo*, and the free amine base may be formed in the tissue cells.

It has been proposed that local anesthetics prevent the depolarization of the nerve membrane that is necessary for the propagation of the nerve impulse. This may be the result of interference with the mutual exchange of sodium and potassium ions across cell membranes. As a consequence, the negative electric potential necessary for a propagated discharge does not develop.

Ritchie and Greengard (1961) reviewed and reinvestigated the subject of the activity of local anesthetics acting as uncharged tertiary amines or as positively charged substituted ammonium ions. They measured the activity of local anesthetics containing a tertiary nitrogen in the molecule on mammalian nonmyelinated fibers of the rabbit's vagus nerve. The compounds studied were dibucaine, tetracaine, chlorpromazine, imipramine, and procaine. Impulse conduction via action potentials was the index of nerve block. From these experiments it was concluded that the active form of the local anesthetic is the cation. This finding differs from the widely held belief that the active form is the uncharged amine.

**Effects of vasoconstrictors on local anes-**

**thesia.** Most local anesthetics do not cause vasoconstriction at the site of injection, as does cocaine. For this reason the addition of a vasoconstrictor to the anesthetic solution will increase the duration of anesthesia. The vasoconstrictor impedes the rapid systemic absorption and tends to reduce the potential toxicity of the drug. In studies on guinea pigs with propoxycaine, procaine, and vasoconstrictors, the duration of local anesthesia was influenced much more by the concentration of the vasoconstrictor than by the concentration of the local anesthetic (Luduena, 1960).

The kind of vasoconstrictor agent and the amount must be properly selected for satisfactory clinical use of local anesthetic solutions. Concentrations of these vascular agents should be kept at the lowest effective level, *e.g.*, 1 part in 130,000 to 1 in 520,000 with epinephrine hydrochloride. Other vasoconstrictors are also used. The use of vasoconstrictor agents in spinal or extradural anesthesia is discussed on page 345.

### Toxicity.

The agents that are used as local anesthetics exert toxic effects if they are absorbed into the general circulation in sufficient concentration. The different drugs vary widely in their toxicity, and some persons are considerably more sensitive to these compounds than others. The rate of injection, the quantity of drug injected, the site of injection, and the action of other drugs present in the local anesthetic solution, along with the age, emotional, and physical condition of the patient, are factors which will determine the development of toxic symptoms. It is a cardinal rule that the dosage of a local anesthetic should be kept as low as possible.

Campbell and Adriani (1958) have shown that the majority of reactions from local anesthetics are due to high plasma drug levels. These excessively high blood concentrations follow the use of undue quantities of drug solutions or rapid absorption. Absorption from the mucous membranes of the pharynx and trachea results in drug blood levels comparable to those found after intravenous injection. Vasoconstrictor drugs do not retard absorption from mucous membranes; they do retard absorption after perineural or subcutaneous injections.

The symptoms produced by acute poisoning with the local anesthetic agents of the procaine type follow in rapid succession. They are *anxiety, fainting, pallor, dyspnea, convulsive seizures* and *respiratory arrest.* When the intoxication occurs by slow absorption of the drug, the foregoing symptoms may be preceded by *laughter, confusion, vertigo* and *palpitation.* Vague sensations are often experienced, such as complete numbness of the legs and cutaneous disturbances resembling the feeling of insects crawling under the skin.

The injection of a local anesthetic solution intravenously may cause the immediate death of the patient, and much care and skill are required to avoid accidental vascular injections. Further, the extensive application of a local anesthetic solution to traumatized mucous membranes or to the urethra may be followed promptly by toxic reactions. It is considered good practice to have available for instant use a quick-acting barbiturate for intravenous injection and an oxygen respirator, in case acute toxicity should result from the administration of a local anesthetic. The administration of pentobarbital by mouth ½ hour before the local anesthetic is injected is a widespread practice.

A number of patients are sensitive to the local anesthetic drugs and will develop a dermatitis when these compounds are used topically. Some idiosyncratic persons may develop a rash following the application of ointments containing one of the local anesthetic drugs. In such cases the use of the material should be discontinued. Constant wetting of the hands with solutions of local anesthetics causes dermatitis in certain individuals. The recent development of local anesthetic drugs, *e.g.*, dyclonine and pramoxine, that do not contain the typical ester and amide linkage of the procaine-type anesthetics, minimizes the danger of cross-sensitivity reactions. This is an advantage in prescribing local anesthetics for topical use.

**Treatment of acute poisoning** is best accomplished by the administration of a quick-acting barbiturate. If the local anesthetic solution has been taken orally, tannic acid solution and gastric lavage are indicated. Alkaloidal antidotes are effective. If the local anesthetic has been injected in an extremity, a tourniquet may be applied. Convulsions may be checked by the intravenous injection of amobarbital sodium or thiopental sodium. In the treatment of acute poisoning a barbiturate would not be indicated if the symptoms were those of depression only. Respiratory stimulants are useful to combat the depressed respiration. Artificial respiration with oxygen may be very effective, since these compounds are detoxified in the tissues.

An interesting illustration of the antagonistic actions of procaine and pentobarbital may be demonstrated in guinea pigs. The effect of procaine on the toxicity of pentobarbital is nearly additive. Procaine increases the sleeping time of guinea pigs narcotized by pentobarbital. On the other hand, pentobarbital diminishes the toxicity of previously administered procaine.

### Properties of a suitable local anesthetic.

To be useful clinically, a local anesthetic should exhibit certain properties. The agent should be freely soluble in water and should produce a solution of suitable concentration which is stable. Heat stability is important, for it permits sterilization of the solutions of the anesthetic agent. The solutions of the local anesthetic should be nearly neutral and should produce a minimal degree of irritation when injected into the tissues. The agent should manifest a specific effect on sensory nerve endings with a minimal effect on surrounding tissue cells. The local anesthetic should be devoid of addictive properties. All of the commonly used agents meet this requirement, with the exception of cocaine. Absorption from the site of injection should be poor. This minimizes systemic toxicity and accentuates the local anesthetic action. In addition, the systemic toxicity should be minimal and if toxicity is manifested, a suitable antidote should be available. The duration of local anesthesia should be controllable by a variation in the concentration of the solution of the anesthetic. Recovery of sensation in the anesthetized area should not be too prolonged after the surgical procedure is completed. The recovery should not leave tissue damage in its wake. It is clear, furthermore, that with all of these admirable properties, a minimal systemic toxicity is of paramount importance. Indeed, with the available local anesthetic agents these aims, for the most part, can be achieved.

**Hyaluronidase** is incorporated with topical local anesthetics to allow the agent freer access to mucosal surfaces, especially in anesthetic gels used in dentistry, gastroscopy, and bronchoscopy. The enzyme also augments local anesthetic action in the eye and in nerve block and infiltration anesthesia. A description of this enzyme, its use, and precautions to be observed when it is used in an infected area are given in Chapter 59.

## Cocaine and Procaine as Local Anesthetics

### Cocaine, N.F.

This alkaloid is obtained from the leaves of *Erythroxylon coca* and other species of *Erythroxylon*, or by synthesis from ecgonine or its derivatives. It is a white, crystalline compound. One gm. of cocaine base dissolves in about 600 ml. of water. Cocaine Hydrochloride, U.S.P., dissolves in ½ of its own weight of water.

Topical application to mucous membranes (*surface anesthesia*) is very effective with cocaine salts. Injection into an area to produce local anesthesia is designated as *infiltration anesthesia.* However, cocaine is not injected because of its toxicity. Cocaine is not effective as a local anesthetic when applied to the intact skin. In the presence of a hyperemia or abrasion of the skin, cocaine and other local anesthetics are active.

**Local ischemia** is produced by cocaine at the site of application. A vasoconstriction is produced that tends to delay the absorption and destruction of the compound. According to some views, cocaine inhibits amine oxidase and hence may prevent the destruction of endogenous epinephrine. Cocaine is the only common local anesthetic that possesses this property. For topical application or injection, a small amount of a vasoconstrictor agent is frequently added to other local anesthetic solutions.

**Effect on adrenergic responses.** A number of experiments indicate that cocaine delays the inactivation of epinephrine and norepinephrine and hence causes a "sensitization" of structures innervated by sympathetic fibers. These experiments, however, do not indicate how the inactivation is delayed. Since cocaine is an amine oxidase inhibitor in some experimental situations, this action has been considered to be responsible for the sympathetic enhancement effects. In a definitive series of experiments Trendelenburg (1959) showed that the sensitizing action of cocaine is not related to a reduction of the liberation of "sympathin." The alkaloid does produce its enhancement effects upon the blood pressure elevation of norepinephrine in direct relation to the increased concentration of norepinephrine in blood plasma, which is elicited by cocainization. The exact mechanism responsible for the inactivation of norepinephrine and the action of cocaine on this process remains to be identified; it is doubtful whether it is related to monoamine oxidase inhibition. It is possible that cocaine inhibits the enzyme *ortho*-methyltransferase that has recently been implicated in the termination of action of epinephrine.

Cocaine augments appreciably the effects of small doses of acetylcholine on the heart rate, blood pressure, and the nictitating membrane in intact, anesthetized animals, according to Koppanyi and Feeney (1959). They suggest that cocaine changes the permeability of cell membranes to ions and that the augmented response to small doses of acetylcholine may be achieved by potentiating circulating epinephrine, since other workers have found acetylcholine effects to be enhanced by the presence of small amounts of epinephrine.

**Duration of anesthesia** depends upon the concentration of the cocaine solution and its method of application. Sensory nerve endings are blocked by low concentrations (0.02 per cent) applied locally. Higher concentrations may produce a local anesthesia lasting 30 minutes or longer.

**Therapeutic use.** Cocaine hydrochloride solution from 2 to 4 per cent is employed in ophthalmic practice for instillation in the eye. *Solutions of this drug are not injected, as less toxic compounds are available for this purpose.* The application of concentrated solutions (5 to 10 per cent) to the mucous membranes of the nose and throat is required for local anesthesia. Cocaine solutions are harmful to the cornea; it may become clouded and pitted following the use of the drug. In addition, cocaine will cause mydriasis. For these reasons cocaine has been replaced as a local anesthetic of importance.

**Toxicology.** Acute poisoning results clinically from overdosage, too rapid absorption, and improper administration of cocaine solutions. The degree of sensitivity of different individuals to cocaine varies greatly. The first effect is one of stimulation of the central nervous system; this in turn is followed by a state of depression. *Hysteria and confusion*, *fullness of the head*, *nausea and vomiting*, *sweating*, *dry throat*, *dilated pupils*, and *vertigo* are symptoms produced by the rapid absorption of cocaine. These symptoms may be followed by a *slow pulse* and a *fall in blood pressure*, *labored respiration* with *clonic* or *tonic convulsions*, *unconsciousness*, *cyanosis*, and *death* by *asphyxia* and *respiratory paralysis*. When a large dose of cocaine has been rapidly absorbed, the symptoms of stimulation may not appear, and depression with approaching respiratory failure may be the chief symptoms.

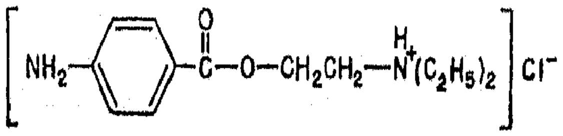
*Chronic cocaine poisoning* or addiction to cocaine is a special public health problem. All derivatives of coca leaves, including the salts of cocaine, fall within the regulations of the Narcotic Laws (see page 393).

In the addict the drug produces a feeling of elation and euphoria, followed by a period of depression and tremors. The incidence of cocaine addiction in the United States is considerably less than in former years. Cocaine "snow" is administered hypodermically or snuffed by habitués. The drug which is sold in the illegitimate traffic is usually highly diluted with inert material.

A description of the use of coca leaf by the natives of Peru and Bolivia is given in the *United Nations Report of the Commission of Enquiry on the Coca Leaf* (1950). The practice is characteristic of the Indian's life in the high Altiplano and Sierra regions and is a part of their whole social structure. Many observers consider coca chewing by the Indians as a form of habituation; others consider it a true addiction. It is obvious that this practice has many social and economic implications and is quite distinct from the addict's use of the alkaloid cocaine in the United States.

### Procaine.

**Procaine Hydrochloride, U.S.P. (Novocain)** is a white, crystalline powder, soluble in water 1:1. The compound is diethylaminoethyl *p*-aminobenzoate hydrochloride.



Procaine Hydrochloride, U.S.P.

Procaine was synthesized by Einhorn in 1905. Procaine has a much lower toxicity than cocaine, and it is not habit forming. It is the most widely used of all local anesthetics.

A solution of procaine hydrochloride is not as rapid in its action as a local anesthetic as cocaine. Among the local anesthetic compounds investigated pharmacologically, an increased anesthetic efficiency is generally associated with an increase in toxicity. When measured by various procedures, procaine elicits an activity which is approximately ⅛ that of cocaine. It is less toxic than cocaine and other commonly used local anesthetic drugs. For infiltration anesthesia it is one of the least toxic anesthetics. When a 2 per cent solution of procaine hydrochloride is injected subcutaneously, it produces a prompt and powerful local anesthetic action. The anesthesia is of short duration, however, unless the solution contains epinephrine or some similar vasoconstrictor agent. The solution is generally nonirritating. The low toxicity of procaine is believed to be the result of its rapid destruction by the esterases in the blood and tissues. Of the numerous derivatives of cocaine and related local anesthetic drugs that have been prepared, procaine is the one most satisfactory for general medical practice.

A solution of procaine hydrochloride has a pH of approximately 6.0; upon standing the solution becomes more acidic. For infiltration anesthesia the compound may be dissolved in physiologic salt solution. The degree of irritation produced upon injection is influenced by tissue osmotic pressure changes, the pH of the solution, and preservatives that may be added to the solution (sodium bisulfite). Numerous salts of procaine have been prepared, including the citrate, tartrate, propionate, isobutyrate, and borate. None of these is superior to the hydrochloride as a local anesthetic for injection. The isobutyrate salt of procaine has been employed by oral administration for the control of nausea, vomiting, and gastritis. Presumably it acts as a surface anesthetic on the lining of the upper gastrointestinal tract.

**Therapeutic use.** For infiltration anesthesia a solution of 0.25 to 1 per cent is prepared in sterile physiologic saline; 0.6 ml. of epinephrine hydrochloride solution (1:1000) is added for each 100 ml. of solution. The 2 per cent Procaine Hydrochloride Injection, U.S.P., may be used for nerve block, 2 per cent Procaine Hydrochloride and Epinephrine Injection, U.S.P., is a preferable dosage form for infiltration anesthesia and nerve block. The dosage for spinal anesthesia is given on page 345.

Buchert (1959) conducted a blind study of the efficacy in dental patients of 0.4 per cent propoxycaine (Ravocaine) and 2 per cent procaine combination with various concentrations of levo-nordefrin, nordefrin, and levoarternol as vasoconstrictors. With levo-nordefrin, 1:10,000 was found to be the most satisfactory concentration, and this vasoconstrictor was preferred. There are numerous vasoconstrictor drugs that are employed in combination with the many local anesthetics.

**Intravenous procaine.** Procaine hydrochloride has been administered intravenously as an analgesic in the treatment of burns, for arthritis, as a substitute for morphine in postoperative care, and in serum sickness. Peterson and his associates (1955) studied the use of intravenous procaine in traumatic pain and the pain associated with inflammatory conditions. They reported that procaine administered in this manner was very effective. The procaine was administered in a 1:1000 concentration in saline. The dosage was 4 mg./kg., administered slowly over a 20-minute period. The symptoms following administration have been described as a sensation of warmth throughout the body, accompanied by flushing of the head and neck, dryness of the mouth, lacrimation, dilation of the pupils, and a sensation of light-headedness. Relaxation usually follows alleviation of pain.

Peterson (1955) extensively investigated the central and peripheral nervous system effects of injecting procaine hydrochloride intravenously. No measurable effect in the functional activity of the various elements of the peripheral nervous system was produced in man. The functional integrity of the reflex arc was not measurably altered in the unanesthetized man or animal when doses of less than 10 mg./kg. were given. Procaine elicited a selective action at the spinal cord level upon synaptic processes of increasing complexity. Procaine was found to produce a selective action on inhibitory descending influences from the brain stem reticular formation. It caused this without blockade of the descending facilitatory influences from the brain stem which affect the motor neuron. In view of these studies,

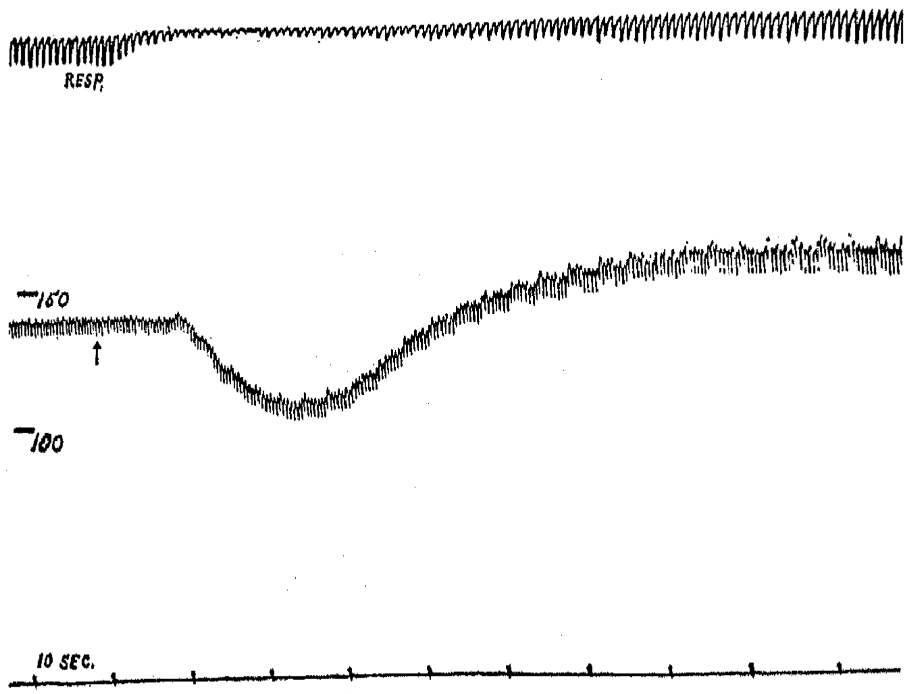


FIG. 17-1. Procaine hydrochloride injection, 1 ml. 2 per cent; given intravenously to 5-kg. dog under ether anesthesia. *Upper tracing,* respiration; *lower tracing,* blood pressure.

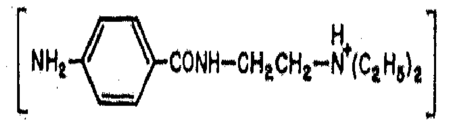
Peterson suggests that in those cases in which intravenous procaine relieves pain, one factor in its action is its effect upon "drug vulnerable reticular relays" which are involved in the pain process.

It appears that the reported success of this therapy in the treatment of intractable pain has been overrated. Controlled studies have demonstrated that the degree of pain relief afforded by intravenously administered procaine is not greater than that afforded by 90 mg. of pentobarbital sodium orally. Indeed, one questions the efficacy of intravenous procaine as an analgesic. It appears that this use of procaine should be considered as one of the less effective measures in the relief of pain (Leake, 1959).

The studies that have been reviewed by the Council on Drugs of The American Medical Association (1962) clearly indicate that procaine has no rejuvenating or beneficial effects in senility and its associated degenerative diseases. Indeed, its use is not without hazard.

Procaine administered intravenously may be dangerous. A number of reports in the literature urge caution in the use of this drug intravenously. Its use is interdicted in *myasthenia* and *thyrotoxicosis,* and in patients on digitalis therapy. Many instances have been reported of fatal anaphylaxis resulting from the use of local anesthetics. In these cases apparently veins were accidentally punctured and relatively small amounts of the anesthetic were introduced into the blood stream of patients who were sensitive to the drug. Preliminary skin tests are unreliable as a means of detecting hypersensitive individuals. Figure 17-1 shows the effects of an intravenous injection of procaine hydrochloride into a dog under ether anesthesia.

Procaine is rapidly hydrolyzed by an esterase which occurs in the blood into *p*-aminobenzoic acid (PABA) and diethylaminoethanol. PABA exhibits no local anesthetic action, and diethylaminoethanol shows only a small fraction of the activity of procaine. Because of the use of intravenous procaine in the treatment of intractable pain and the prevention of cardiac arrhythmias, similar compounds were sought to prolong the action of procaine by modification of the molecule. A compound which was found most satisfactory resulted from the removal of one oxygen atom from procaine and replacement by an amine group. Its structure is shown in the accompanying formula.



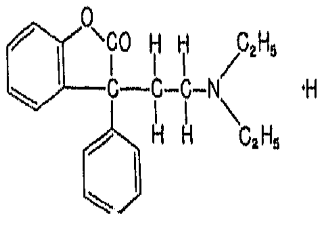
Procainamide Hydrochloride, U.S.P., Pronestyl

This compound was found to be refractory to hydrolysis. Its local anesthetic properties were about equal to those of procaine. The therapeutic use of procainamide in the treatment of ventricular arrhythmias is discussed on page 660.

## Other Soluble Local Anesthetics

### **Amolanone hydrochloride (Amethone).**

Amolanone is 3-(β-diethylaminoethyl)-3-phenyl-2-benzofuranone hydrochloride.



Amolanone Hydrochloride

Amolanone is a local anesthetic with anticholinergic actions. Because this drug proved to have marked antispasmodic properties, it was originally used systemically in ureteral colic caused by calculi and in the relief of spasm of the ureter and urinary bladder. At the present time its use is confined to topical anesthesia of the lower urinary tract.

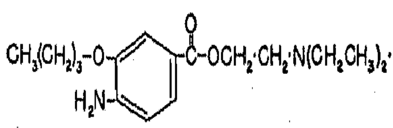
Amolanone hydrochloride occurs as a crystalline powder. It is very soluble in water.

For intraurethral instillation before urologic procedures, a 0.33 per cent solution of amolanone hydrochloride is employed. The drug solution is not injected. The anesthetic effects generally are produced within 5 minutes and last for 15 to 30 minutes. Not all reports have indicated satisfactory results with this local anesthetic.

The drug solution is not irritating, although a transitory burning sensation is sometimes experienced by the subject. Appreciable amounts of the drug are not absorbed, and only isolated instances of slight giddiness have been reported. Because this local anesthetic is apparently effective and relatively nontoxic, its future trial is indicated in urologic procedures.

### **Benoxinate Hydrochloride, U.S.P. (Dorsacaine).**

This drug is β-diethylaminoethyl 4-amino-3-*n*-butoxybenzoate hydrochloride.



Benoxinate Hydrochloride, U.S.P.

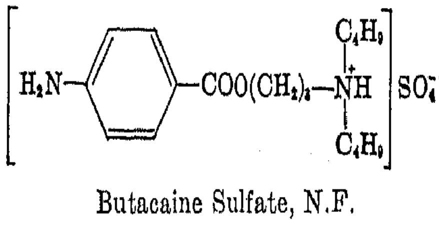
It is a colorless, crystalline powder, freely soluble in alcohol and water.

This local anesthetic is administered only by topical instillation in the eye. It has slight bacteriostatic properties. By local application to the eye in the form of a 0.4 per cent solution, the anesthetic elicits a somewhat more intense effect than comparable solutions of tetracaine hydrochloride. One drop of a 0.4 per cent solution is considered adequate for tonometry. The drug is used in gonioscopy, for the removal of foreign bodies from the cornea, and for short operative procedures upon the cornea and conjunctiva. Benoxinate Hydrochloride Ophthalmic Solution, U.S.P., is a 0.4 per cent solution.

In experimental animals this local anesthetic has about the same toxicity as cocaine upon intravenous injection.

### **Butacaine Sulfate, N.F. (Butyn sulfate).**

Butacaine sulfate is 3-(*p*-aminobenzoxy)-1-di-*n*-butylaminopropane sulfate.



Butacaine Sulfate, N.F.

It is a white, crystalline powder. It dissolves slowly in less than its own weight of water.

This local anesthetic is particularly effective in surface anesthesia for the eye, nose, and throat. It is more effective than cocaine and is more toxic. It has been employed most successfully as a local anesthetic for operations on the eye. It is generally used in 1 per cent solution. Butyn sulfate ointment, 1 per cent, is a useful local anesthetic ointment.

Butacaine sulfate must be employed with great caution when injected as a local anesthetic. The dosage is less than that of cocaine and procaine, and the physician must be prepared to combat the symptoms of acute poisoning that may arise from the accidental entry of the drug into the general circulation.

### **Butethamine Hydrochloride, N.F. (Monocaine).**

This white, odorless, fine crystalline powder is soluble in water to the extent of 3 per cent. Its solutions are bitter and produce anesthesia when applied to the tongue. The compound is 2-isobutylaminoethyl *p*-aminobenzoate hydrochloride.

Butethamine hydrochloride is a local anesthetic possessing properties similar to those of procaine. It is somewhat more active as a surface anesthetic than procaine but is inferior to cocaine or butacaine for this purpose. It is used as a local anesthetic for nerve block anesthesia in dentistry.

Butethamine hydrochloride has been reported to be about 1.6 times as toxic as procaine hydrochloride when injected intravenously into guinea

TABLE 17-1

*Commonly Used Local Anesthetics*

| Official Name | Status | Manufacturer's Trade Name | Methods of Application |
|---|---|---|---|
| Amolanone Hydrochloride | N.N.D. | Amethone | Urologic procedures |
| Benoxinate Hydrochloride | N.N.D. | Dorsacaine | Topical in eye only |
| Butacaine Sulfate | N.F. | Butyn | Surface |
| Butethamine Hydrochloride | N.F. | Monocaine | Infiltration |
| Butethamine Formate | N.N.D. | Monocaine | Caudal, spinal |
| Butyl Aminobenzoate | N.F. | Butesin | Topical |
| Chloroprocaine Hydrochloride | N.N.D. | Nesacaine | Infiltration, epidural, caudal |
| Cyclomethycaine Sulfate | N.N.D. | Surfacaine | Topical |
| Cocaine Hydrochloride | U.S.P. | | Surface, infiltration |
| Dibucaine Hydrochloride | U.S.P. | Nupercaine | Infiltration, surface, caudal, spinal |
| Dimethisoquin Hydrochloride | N.F. | Quotane | Surface |
| Dyclonine Hydrochloride | N.N.D. | Dyclone | Topical |
| Ethyl Aminobenzoate | N.F. | Benzocaine | Topical |
| Hexylcaine Hydrochloride | N.F. | Cyclaine | Surface, spinal, caudal, infiltration |
| Lidocaine Hydrochloride | U.S.P. | Xylocaine | Infiltration, surface, caudal |
| Mepivacaine Hydrochloride | N.N.D. | Carbocaine | Infiltration, caudal |
| Naepaine Hydrochloride | N.F. | Amylsine | Surface |
| Parethoxycaine Hydrochloride | N.N.D. | Intracaine | Infiltration, spinal |
| Phenacaine Hydrochloride | N.F. | Holocaine | Surface |
| Piperocaine Hydrochloride | U.S.P. | Metycaine | Surface, caudal, infiltration |
| Pramoxine Hydrochloride | N.F. | Tronothane | Topical |
| Procaine Hydrochloride | U.S.P. | Novocaine | Infiltration, spinal |
| Proparacaine Hydrochloride | N.N.D. | Ophthaine | Topical in eye only |
| Propoxycaine Hydrochloride | N.F. | Ravocaine | Infiltration |
| Tetracaine Hydrochloride | U.S.P. | Pontocaine | Surface, spinal, caudal |

pigs. It possesses about ⅓ more anesthetic potency than procaine.

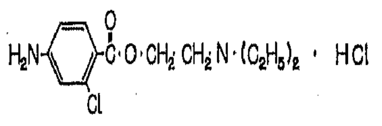
For dental or other minor surgery a solution of butethamine hydrochloride greater than 1 per cent should not be employed. A solution of 1.5 per cent butethamine hydrochloride in 1:100,000 epinephrine may be used when adequate depth of anesthetic effect cannot be obtained by the 1 per cent solution or for major surgery.

**Butethamine Formate** has been proposed for use as a spinal anesthetic. This salt possesses an anesthetic action qualitatively identical with that of procaine. Quantitatively it may produce about ⅓ greater anesthetic and toxic effects than procaine.

### Chloroprocaine Hydrochloride (Nesacaine).

Chloroprocaine is $\beta$-diethylaminoethyl 2-chloro-4-aminobenzoate hydrochloride.

Chloroprocaine is more rapid in onset of action, and its potency is approximately twice that of procaine. It does not produce vasoconstriction; therefore epinephrine must be used in the preparation of solutions for local anesthesia. Plasma cholinesterase will hydrolyze chloroprocaine in the same manner it hydrolyzes procaine, and the hydrolysis is more rapid.

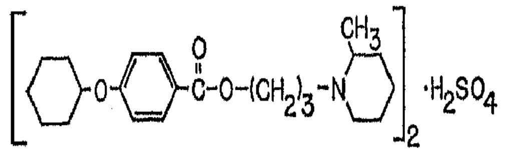


Chloroprocaine Hydrochloride

Chloroprocaine is not active as a topical local anesthetic for application to the skin or mucous membranes. It is used for infiltration anesthesia, field block, and regional nerve block (epidural and caudal) anesthesia. For infiltration anesthesia a solution is prepared containing 1 per cent chloroprocaine and 1:200,000 epinephrine hydrochloride. From 2 to 75 ml. of this solution is injected, depending upon the extent of the area to be anesthetized and the injection site. A 2 per cent solution is usually employed for extradural sacral block anesthesia.

### Cyclomethycaine Sulfate (Surfacaine).

This drug is 3-(2-methylpiperidino)-propyl-*p*-cyclohexyloxybenzoate sulfate.



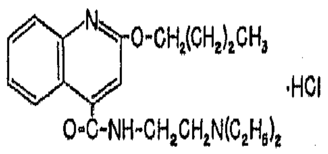
Cyclomethycaine Sulfate

Cyclomethycaine sulfate is used as a topical anesthetic on the abraded skin, mucous membranes, rectum, vagina, and urethra. It is not very effective in the eye or ear and relatively weak in its effects on the mucous membranes of the mouth, nose, trachea, or bronchi.

Cyclomethycaine sulfate is applied topically to the skin as a 0.25 per cent aerosol, a 0.5 per cent cream, or a 1.0 per cent ointment. The drug is administered as 10-mg. rectal suppositories or in the form of a 0.75 per cent urethral jelly for topical local anesthesia. Cyclomethycaine may cause symptoms of mucosal or dermal sensitivity.

### Dibucaine Hydrochloride, U.S.P. (Nupercaine).

This drug is 2-*n*-butoxy-N-(2-diethylaminoethyl)cinchoninamide hydrochloride.



Dibucaine Hydrochloride, U.S.P.

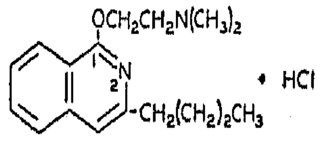
It is a colorless, crystalline powder, freely soluble in water and alcohol.

Dibucaine is a potent but toxic local anesthetic. It is approximately 12 times as toxic as cocaine upon subcutaneous injection and 6 times as toxic after intravenous injection in experimental animals. Its extreme potency permits the use of very dilute solutions in local anesthesia.

For infiltration anesthesia a 0.05 to 0.1 per cent solution is employed with epinephrine hydrochloride 1:200,000. The total amount injected should not exceed 100 ml. Because of its high toxicity the drug must be used with great care. When applied topically to mucous membranes, the drug promptly produces anesthesia of the tissues which persists for long periods.

### Dimethisoquin Hydrochloride, N.F. (Quotane).

This drug is 3-butyl-1-(2-dimethylaminoethoxy) isoquinoline hydrochloride.



Dimethisoquin Hydrochloride, N.F.

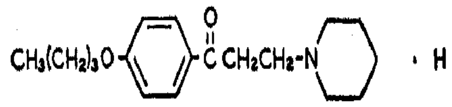
It is a colorless, white powder, freely soluble in alcohol and water.

Dimethisoquin is more potent than procaine as a local anesthetic, and it is believed to be less likely to produce sensitization reactions. Its toxicity is greater than that of procaine or cocaine. This local anesthetic is not used for injection purposes but is applied topically.

In the form of a 0.5 per cent lotion or ointment, the drug is useful in the relief of itching, irritation, burning, or pain associated with the dermatosis.

### Dyclonine Hydrochloride (Dyclone).

Dyclonine is 4′-butoxy-3-piperidinopropiophenone hydrochloride.



Dyclonine Hydrochloride

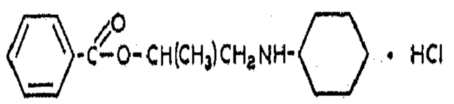
It is a colorless, crystalline powder, soluble in water.

Dyclonine is an organic ketone and does not contain the usual ester or amide linkage typical of the procaine-type local anesthetics. Its toxicity is low, and the incidence of sensitivity reactions is said to be less than 0.1 of 1 per cent.

Applied topically as a 1 per cent cream or as a 0.5 per cent solution to the skin or mucous membranes, the drug produces a profound anesthesia that usually lasts for 45 minutes. At the present time its use is restricted to topical application, and it is not injected.

### Hexylcaine Hydrochloride, N.F. (Cyclaine).

Hexylcaine is 1-cyclohexylamino-2-propyl benzoate hydrochloride



Hexylcaine Hydrochloride, N.F.

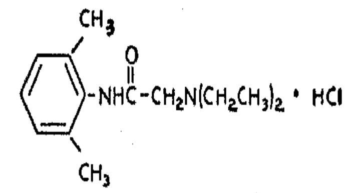
It is a colorless, bitter powder with a slight aromatic odor. It is freely soluble in alcohol and water.

Hexylcaine is approximately equivalent to cocaine as an anesthetic when applied topically. In infiltration anesthesia its action is more rapid in onset and is longer lasting than procaine. This drug shares the toxic qualities of the other local anesthetics, and established precautions in its use must be observed.

For infiltration anesthesia from 5 to 65 ml. of a 1 per cent solution is used. For surface anesthesia concentrations up to 5 per cent may be applied topically. This drug is employed in spinal anesthesia, and special technics are used in preparing the solution for injection.

### Lidocaine Hydrochloride, U.S.P. (Xylocaine Hydrochloride).

This substance is a local anesthetic that was developed by Löfgren (1948). This investigator prepared a large number of compounds related to lidocaine and after extensive physicochemical, pharmacologic, and clinical studies found lidocaine to be a superior local anesthetic agent. Lidocaine is 2-diethylamino-2′,6′-acetoxylidide hydrochloride.



Lidocaine Hydrochloride, U.S.P.

In the relatively short time since its introduction lidocaine has become a most popular local anesthetic; in many clinics it is now the local anesthetic of choice, replacing procaine.

Lidocaine is active in surface anesthesia as well as upon injection. Löfgren (1948) compared lidocaine with procaine and found that lidocaine had a shorter latency period and produced longer duration of anesthesia with a lower relative toxicity. Lidocaine hydrochloride is 3.3 times as active as procaine, using minimal effective concentration as a criterion. These results were obtained on the sciatic-nerve-leg preparation of *Rana arvensis.*

In mice a 0.5 per cent solution of lidocaine hydrochloride has about the same toxicity as procaine hydrochloride. As the concentration of lidocaine hydrochloride increases to 2 per cent, the toxicity exceeds that of procaine hydrochloride. Various values have been reported for the relative toxicities of the two local anesthetics. The clinical significance of these facts is not clear. The liver is the chief site of biotransformation of lidocaine, and the free and conjugated forms of the drug are excreted in the urine of animals and man.

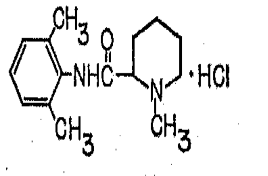
Clinically, lidocaine hydrochloride produces more prompt, intense, and extensive anesthesia than procaine hydrochloride. It is compatible with epinephrine hydrochloride. It can, however, be used without epinephrine hydrochloride. It is useful for infiltration and block anesthesia. It is also effective topically when applied to mucous membranes and to the peritoneal cavity, with a latent period of as long as 5 minutes. It has been employed for continuous caudal, peridural, and spinal (subarachnoid) anesthesia with satisfactory results. These technics are discussed in Chapter 22.

Morrisset (1957) reported what is believed to be the first anaphylactic death from lidocaine after the injection of 0.8 ml. of a 2 per cent solution with 1:50,000 epinephrine hydrochloride for a dental procedure. Toxic reactions to lidocaine are generally characterized by extreme depression, in contrast to adverse procaine reactions, which are excitatory in character. Side reactions to lidocaine hydrochloride are rare. Nausea, twitching, and chills have been observed. Generalized convulsions have been reported following repeated lidocaine injections. The convulsions may be preceded by a brief period of unconsciousness (DiGiovanni, 1963).

Lidocaine Hydrochloride Injection, U.S.P., is a sterile solution for infiltration anesthesia in a 0.5 per cent concentration; for block anesthesia and for topical use a 1 to 2 per cent concentration is recognized. A 5 per cent lidocaine ointment and a 2 per cent jelly are commercially available. For routine use in dental practice 2 per cent lidocaine with epinephrine hydrochloride 1:100,000 is recommended.

### Mepivacaine Hydrochloride (Carbocaine).

This local anesthetic belongs chemically to the xylidide series. Lidocaine is closely related to mepivacaine. Mepivacaine is *d,l*-N-methylpipecolic acid 2,6-dimethylanilide.



Mepivacaine Hydrochloride

The hydrochloride salt is a colorless, crystalline powder, readily soluble in water. Mepivacaine in solution is resistant to both alkaline and acid hydrolysis. It may be boiled for several hours without decomposition. The optical isomers are equivalent in anesthetic potency and toxicity; therefore the racemic form is marketed as Carbocaine.

Mepivacaine is a relatively nontoxic local anesthetic that resembles lidocaine in potency. Reports differ on its efficacy in various types of local anesthesias as compared to lidocaine. In a blind comparative study in endodontia and exodontia, Gruber (1962) found lidocaine superior in intensity of anesthesia and frequency of satisfactory operative anesthesia. Mepivacaine hydrochloride 2 per cent with levonordefrin 1:20,000 was compared with lidocaine hydrochloride 2 per cent with epinephrine hydrochloride 1:100,000.

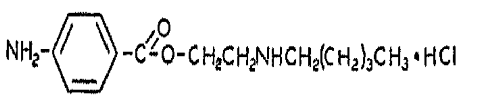
Mepivacaine exerts its local anesthetic action without the addition of vasoconstrictor agents. However, it is frequently employed in combination with levonordefrin. In 1 per cent solutions in mice the anesthetic potency of mepivacaine was slightly greater and longer-acting than lidocaine, and about twice as potent as procaine. In general, this relationship appears to hold in man.

In infiltration and nerve block anesthesia 1 or 2 per cent sterile saline solutions of mepivacaine hydrochloride are used. A total dose of 20 ml. should not be exceeded. For caudal and peridural block from 15 to 30 ml. of a 1 per cent solution is employed.

The safety of mepivacaine appears to resemble that of lidocaine. The adverse reactions are similar to those produced by the other local anesthetics, and the same precautions must be observed. There is insufficient information to determine the safety or efficacy of mepivacaine for intrathecal use. Mepivacaine may be considered less hazardous as a local anesthetic in elderly or hypertensive patients or in subjects with cardiovascular disease. In these persons the addition of epinephrine or a similar vasoconstrictor agent to the local anesthetic solution may be undesirable. The local anesthetic action of mepivacaine can be obtained without such an agent.

### Naepaine Hydrochloride, N.F. (Amylsine).

This substance is 2-amylaminoethyl *p*-aminobenzoate hydrochloride.



Naepaine Hydrochloride, N.F.

It is a colorless, crystalline powder, sparingly soluble in alcohol but soluble in water.

This local anesthetic is used in ophthalmology to produce corneal anesthesia without mydriasis; 1 to 2 drops of a 2 to 4 per cent solution instilled in the eye is usually sufficient to produce the desired degree of anesthesia for the relief of superficial pain.

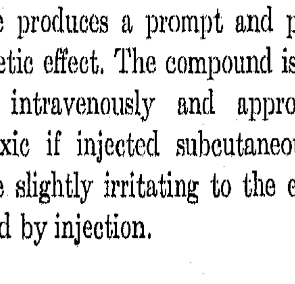
### Parethoxycaine Hydrochloride (Intracaine).

This drug is 2-diethylaminoethyl-*p*-ethoxybenzoate hydrochloride. As a local anesthetic parethoxycaine is somewhat more potent and more toxic than procaine. It is pharmacologically similar to procaine and has similar local anesthetic actions. It should be employed with the same limitations for clinical use as are recognized for procaine.

For regional anesthesia by infiltration, a 0.3 to 1 per cent solution is used. For nerve block, a 1 to 1.5 per cent solution is recommended. In most dental procedures a 1 per cent solution with 1:200,000 epinephrine hydrochloride has been used. A 2.5 per cent solution is employed for spinal anesthesia.

### Phenacaine Hydrochloride, N.F. (Holocaine Hydrochloride).

This compound is bis-*p*-ethoxyphenylacetamidine hydrochloride. The compound is a white, crystalline powder, soluble in water 1:50.

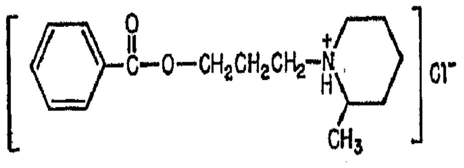


Phenacaine Hydrochloride, N.F.

The chief advantage of this anesthetic is its prompt action. A 1 per cent solution instilled into the eye produces a prompt and prolonged local anesthetic effect. The compound is as toxic as cocaine intravenously and approximately twice as toxic if injected subcutaneously. Its solutions are slightly irritating to the eye. It is not employed by injection.

**Piperocaine Hydrochloride, U.S.P. (Metycaine hydrochloride).**

Piperocaine hydrochloride occurs as a white, crystalline, odorless powder. It is freely soluble in water.

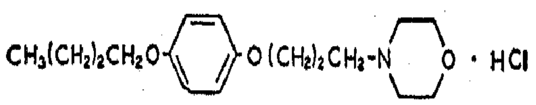


Piperocaine Hydrochloride, U.S.P.

Solutions of piperocaine produce prompt anesthesia by topical application to mucous membranes or by subcutaneous injection. The subcutaneous toxicity of piperocaine is comparable to that of procaine. Intravenously, however, the toxicity of piperocaine is approximately 3 times greater than that of procaine. As a spinal anesthetic, piperocaine appears to be comparable to procaine. Solutions of 1 to 4 per cent of the agent are used for infiltration anesthesia, and 0.5 to 1 per cent solutions are employed for nerve block procedures.

**Pramoxine Hydrochloride, N.F. (Tronothane).**

Pramoxine is 4-[3-(*p*-butoxyphenoxy)-propyl] morpholine hydrochloride.



Pramoxine Hydrochloride, N.F.

It is a colorless, crystalline powder, freely soluble in alcohol and in water.

This is a topically applied local anesthetic, chemically different from the benzoate ester-procaine type. Its dissimilar structure may make it useful in patients sensitive to the usual type of local anesthetics. *The drug is irritating if injected; for this reason its use is restricted to the skin. It is not used on the mucous membranes of the nose or eyes.*

Pramoxine is applied topically in a 1 per cent concentration as a cream, jelly, or solution. It may be employed to relieve itching associated with dermatoses and to anesthetize laryngopharyngeal surfaces prior to instrumentation. The solution may be employed to facilitate endotracheal and intragastric intubation. It is not used in bronchoscopic procedures.

**Proparacaine Hydrochloride (Ophthaine).**

This compound is 2-diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride. It differs chemically from procaine and related local anesthetics in that the amino group on the benzoic acid ester ring is in the *meta* rather than the *para* position. It has been proposed that this difference may explain the lack of cross-sensitization between this anesthetic and other compounds.

Proparacaine is used as a surface anesthetic in ophthalmology. Its anesthetic potency is somewhat greater than tetracaine. It is administered only by instillation in the eye as a 0.5 per cent solution. Surface anesthesia is produced within about 20 seconds after the instillation of 1 or 2 drops of the solution. This permits tonometry to be performed. Anesthesia lasts for about 15 minutes. For deep anesthesia 1 drop is instilled in the eye every 5 to 10 minutes for 5 to 7 doses.

**Propoxycaine Hydrochloride, N.F., (Ravocaine).**

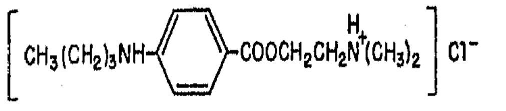
This compound is 2′-diethylaminoethyl-2-propoxy-4-aminobenzoate hydrochloride. Like procaine hydrochloride, the aqueous solutions of propoxycaine are stable and very slightly acid, pH 5.5. The solution may be adjusted to pH 7.0 without the precipitation of the free base.

By using the intracutaneous wheal test on the guinea pig, propoxycaine was found to be nearly 3 times more potent than lidocaine and 9 times more potent than procaine. The toxicity of propoxycaine is approximately 3 times greater than that of lidocaine and about 9 times greater than that of procaine. Thus again one finds in this series of local anesthetics of the *p*-aminobenzoic acid type a parallelism between toxicity and anesthetic activity. Propoxycaine is reported to be about one-half as irritating to tissues as is lidocaine.

Propoxycaine hydrochloride used for nerve block and infiltration anesthesia is available as a 0.5 per cent solution in sterile isotonic saline. In clinical use it is said to be quick acting and to provide a prolonged local anesthesia 2 to 3 times that of procaine. The usual amount employed is 2 to 5 ml. of the 0.5 per cent solution. Amounts up to 20 ml. may be injected if proper precautions are observed.

**Tetracaine Hydrochloride, U.S.P. (Pontocaine hydrochloride).**

This is a white, crystalline, odorless powder. It is very soluble in water. It is 2-dimethylaminoethyl *p*-butylaminobenzoate hydrochloride.



Tetracaine Hydrochloride, U.S.P.

In concentrations of 0.5 to 2 per cent tetracaine is more powerful than procaine or cocaine. The 0.5 and 1 per cent solutions have proved equal in anesthetic potency to 5 and 10 per cent solutions of cocaine. A 0.5 per cent solution is used in the eye.

Tetracaine hydrochloride does not produce the vasoconstrictor action of cocaine. When necessary, epinephrine hydrochloride may be added to produce vascular constriction. When applied to the nose and throat, tetracaine hydrochloride exhibits a marked and persistent anesthetic action.

When the solution is sprayed into the trachea, *the amount should not exceed 1 ml. of 2 per cent solution of tetracaine hydrochloride.* To prevent entrance of the solution into the lungs, the patient should be instructed not to inhale deeply during administration. In order to avoid entrance into the bronchi and rapid absorption from the alveoli, the solution should not be administered by forceful injection.

A 1 or 2 per cent solution has proved useful for abolishing the laryngeal and esophageal reflexes and for bronchoscopy and esophagoscopy. For this purpose the amount should not exceed 2 ml. of 1 per cent solution or 1 ml. of 2 per cent solution.

Toxic reactions following the use of tetracaine hydrochloride for bronchoscopy have been observed. Such side effects may be manifestations of an existing allergic hypersensitivity. Fortunately, serious reactions are rare; however, some have terminated fatally. In isolated instances the untoward effects were due to overdosage.

The use of this drug as a spinal anesthetic is discussed on page 345.

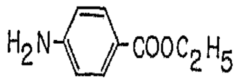
### SLIGHTLY-SOLUBLE LOCAL ANESTHETICS

The limited solubility of a number of local anesthetic compounds in water renders them unsuitable for injection purposes. However, applied topically to ulcers, wounds, and mucous surfaces, these compounds are poorly absorbed; hence they are safer for use than the salts of the water-soluble local anesthetics. Generally speaking, the anesthesia which they produce is not so intense as the soluble local anesthetics but is more lasting. The slightly-soluble local anesthetics are employed therapeutically in the form of dusting powders, dissolved in oils, or as ointments in either a petrolatum or a water-soluble ointment base.

These compounds may produce a dermatitis in some individuals. As a class, however, they are generally nonirritating and nontoxic.

**Ethyl Aminobenzoate, N.F. (Benzocaine).**

This white, crystalline powder is odorless and tasteless and almost insoluble in water (1:2500); its chemical constitution is shown in the accompanying formula:



Ethyl Aminobenzoate, N.F.

Ethyl aminobenzoate is about $\frac{1}{20}$ as toxic as cocaine hydrochloride. It is not absorbed to any appreciable extent when applied topically in the form of a dusting powder or ointment.

**Ethyl Aminobenzoate Ointment, N.F.,** is a 5 per cent ointment of the compound in white ointment base. This ointment is employed for its local anesthetic action on abraded and denuded areas of the skin.

**Butyl Aminobenzoate, N.F. (Butesin).**

This compound occurs as a white, crystalline, very slightly soluble powder. It is odorless and tasteless. The compound is *n*-butyl *p*-aminobenzoate.

Butyl aminobenzoate is employed as an insoluble local anesthetic dusting powder. It may be diluted with a suitable powder such as talc or used directly. The compound is soluble in oils and fatty ointment bases. It is a useful local anesthetic when employed in the form of troches, suppositories, or ointments. Butyl aminobenzoate is claimed to be more effective than ethyl aminobenzoate as a local anesthetic.

**Butesin picrate** is a compound consisting of 1 molecule of trinitrophenol and 2 molecules of the normal butyl ester of 4-aminobenzoic acid. It is a yellow, amorphous powder, soluble in water to the extent of 1:2000. The compound is di-(*n*-butyl *p*-aminobenzoate) trinitrophenol. It is employed almost exclusively in the treatment of minor burns in the form of a 1 per cent ointment with nitromersol, 1:5000.

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# 18

# *The Local Use of Drugs in Eye, Ear, Nose, and Throat*

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Numerous drugs used in the treatment of disease are employed by local applications to the mucous membranes of the eye, ear, nose, and throat. Many of the drugs so used, such as atropine and epinephrine, have systemic pharmacologic actions and are discussed under other headings. In this chapter the topical use of many of these drugs and other agents in the local treatment of eye, ear, nose, and throat affections is discussed.

## THE USE OF DRUGS IN THE NOSE

**Rationale of local nasal medication.** With few exceptions the local use of medications in the nasal passages is for the relief of symptoms and not as specific therapy to eradicate disease. The aim of such preparations is thus the restoration of the normal physiology of the nose.

The entire respiratory tract is lined with ciliated epithelium, and the epithelium of the nose and paranasal sinuses is especially endowed with the capacity of constantly propelling a blanket of mucus in the direction of the nasopharynx. This mucous layer is an effective trap for bacteria and other inhaled particulate matter. Bacteria sprayed into the nasal cavity are rapidly swept away in this mucus. The eradication of pathogenic bacteria in the nasal cavity by local medication, although sometimes desirable, is seldom necessary if the cilia and mucous blanket are functioning normally.

The mucous secretion of the nose is normally acid (pH 5.5 to 6.5), and this acidity has rather marked bacteriostatic action for many pathogens. A change in pH in either direction promptly slows or stops the ciliary activity. Infection, allergy, trauma, sudden changes in temperature, and the entrance of irritating substances into the nasal cavities all cause a prompt change in the pH of the mucus, usually toward the alkaline side. Concomitantly the turbinal tissues exhibit immediate swelling and turgescence with manifest obstruction to breathing as a reflex protective mechanism.

Because ciliary activity is a normal physiologic protective mechanism, it is imperative that the medication should interfere with it as little as possible. For example, ciliary activity continues unimpeded in the presence of normal salt solution. However, hypertonic and hypotonic sodium chloride solutions interfere with ciliary activity and may block it completely. Ephedrine sulfate solutions up to 3 per cent concentration in saline do not inhibit ciliary activity if they are isotonic. Liquid petrolatum, on the other hand, although it does not block the ciliary activity, lies as a covering over the mucous blanket and retards the action of the cilia. Preparations with an oily base are undesirable.

Kimura (1959) has developed an experimental technic for estimating the effects of drugs upon ciliated epithelium. Employing ciliary motility and cellular structure of the rat trachea, the dose causing cessation of ciliary motility in 50 per cent ($ED_{50}$) of rat tracheal rings after 5 minutes immersion is calculated. Of a number of local anesthetic agents procaine was least toxic; phenylephrine solution did not effect ciliary motion.

Ideally, preparations for local application to the nasal cavities should be aqueous, isotonic, slightly acid with a high buffer capacity, and should not impair ciliary activity.

**Systemic effects from nasal medication.** Local medication to the nasal passages may elicit systemic effects through absorption of the drug. For example, in the treatment of diabetes insipidus the insufflation of posterior pituitary powder permits its absorption from the nasal mucosa and thus is useful in the control of the symptoms of the disease. The use of strong solutions of cocaine hydrochloride on the nasal membranes must be enjoined with great caution because of the possibility of concomitant toxic systemic effects. Corticotropic substances may likewise be absorbed by the nasal mucosa and exert systemic effects. Conversely, useful pharmacologic effects may be achieved in the nasal passages by the oral or parenteral use of medicaments, such as the oral use of ephedrine in allergic rhinitis.

**Nasal drug dosage forms.** Most medications are applied to the nasal passages in the form of drops, as an "atomized vapor" or as an aerosol. Dropper application of nasal medication does not distribute the solution effectively through the nasal passages, and frequently dangerous quantities of the drug are ingested.

**Aerosols** are stable suspensions of liquid or solid particles in a gas such as air or oxygen. Coarse liquid sprays used for the nose and throat are produced with *atomizers*. These sprays are unstable suspensions and never reach the bronchi. *Nebulizers* are special devices for reducing the particles to sizes ranging from 30 to 0.5 microns. These are relatively stable suspensions and penetrate the bronchi and reach even alveoli.

In the liquid aerosols, aqueous solutions are used to dissolve the drug, and a fine stable mist is formed. This mist increases the relative humidity which aids in liquefying secretions and ameliorating local dehydration. Various detergents are often added to the liquid. These reduce surface tension and thus facilitate the production of the aerosol. They also aid in liquefying and emulsifying secretions of the broncho-pulmonary tree.

*Alevaire* is an aqueous solution of a mucolytic detergent designed to be administered as an aerosol for the treatment of various types of chronic pulmonary diseases characterized by highly viscid sputum. It contains 0.125 per cent superinone, an oxyethylated tertiary octylphenol-formaldehyde polymer as a surface-active detergent, 2 per cent sodium bicarbonate and 5 per cent glycerin.

This agent has been used in asthmatic cases where copious secretions or mucous plugs obstructed a free airway, in emphysema from various causes, and in the treatment of the respiratory effects resulting from burns and the inhalation of noxious fumes. This aerosol therapy may be employed in the treatment of neonatal asphyxia when breathing difficulties of any type are encountered. Alevaire aerosol therapy is used in croup, laryngitis, pertussis, poliomyelitis, sinusitis, postoperative pulmonary complications, and in routine oxygen administration. The results have been favorable, and it appears that this type of medication is exceedingly beneficial in relieving many kinds of bronchial irritation and partial obstruction.

The mechanism of action of Alevaire appears to be related to 2 factors, humidification of the inspired air and the liquefying effects of the detergent on mucopurulent secretions. Aerosols of the substance are inhaled deeply so that physical contact is made in the finer bronchioles and alveolar ducts. Thick, viscid mucus which partially blocks the airway is liquefied. The surface tension and viscosity of the secretions are lowered; the frictional forces required for propelling the mucus by the cilia, bronchiolar peristalsis, and coughing are likewise reduced. A more normal respiratory airway can be maintained, and the hazards of atelectasis, emphysema, and infection are decreased.

The most satisfactory administration of Alevaire requires a compressed gas and a suitable nebulizing device. As its action is largely physical, it is necessary that a very fine aerosol be inhaled. Hand bulb nebulizers are not adequate, but several types of simple aerosolizing devices are available.

Toxic reactions following the clinical use of Alevaire have not been reported. The surface-active agent in Alevaire is nonhemolytic in the concentrations employed. Animals have lived their life span in a mist of this agent and not developed toxic effects. *In vitro* studies using isolated human adenoid tissue and animal tracheae have indicated that Alevaire does not change ciliary activity.

Because of the wetting, penetrating, and spreading properties of Alevaire, it has been used effectively as a vehicle for the administration of antibiotics, bronchodilators, decongestants, and topical anesthetics to the mucosal surfaces of the respiratory tract.

*Tergemist* is a mucolytic detergent solution for administration as an aerosol. It is an aqueous solution containing 0.125 per cent sodium 2-ethylhexyl sulfate as a detergent and 0.1 per cent potassium iodide. The solution is nebulized and used in the treatment of various types of pulmonary disease characterized by thick, tenacious sputum. It is employed in essentially the same manner as Alevaire. The recommended dose of Tergemist is 3 to 5 ml. of the solution nebulized and inhaled for periods of ½ hour 4 times daily.

Tergemist has been used with some benefit in the treatment of postoperative atelectasis. As both Tergemist and Alevaire appear to afford some relief in experimental pulmonary edema in animals, these agents may merit trial in man.

*Acetylcysteine* (*Mucomyst*). The removal of thick or tenacious mucus in the *lower* respiratory tract is difficult. These abnormal secretions are associated with acute and chronic bronchitis, bronchiectasis, pneumonia and the complications of tuberculosis, ruptured lung abscess, and cystic fibrosis. The discovery of the mucolytic properties of L-cysteine led to the development of acetylcysteine as a therapeutic product effective in treating these conditions. This substance probably exerts its mucolytic activity through the free sulfhydryl group acting upon the disulfide bonds present in mucus (Sheffner, 1963). The sulfhydryl-disulfide interchange reaction is believed to cause an opening of the disulfide bonds in mucoprotein. This action causes the viscosity of thick mucus to be reduced. A number of disulfide bond-cleaving agents, *e.g.*, penicillamine, produce this effect on the viscosity of macroglobulin solutions.

Acetylcysteine is available as a sterile, 20 per cent solution. It may be diluted and used as an aerosol or nebulized into a face mask, mouthpiece, or tracheostomy tube. The recommended dose is 3 to 5 ml., 3 to 4 times a day. The technics of administration vary, depending upon the nature of the clinical indication.

The reduction in viscosity of the bronchial secretions in acute bronchopulmonary conditions is most marked. In a wide variety of acute and chronic suppurative pulmonary diseases, Webb (1962) reported the substance to be extremely effective with almost no associated complications. In treating tracheobronchial secretions in cases of cystic fibrosis, Reas (1963) noted that acetylcysteine produced a greater reduction in the viscosity of the secretions than did 2 control aersols. Special precautions are necessary when the increased volume of liquefied bronchial secretions occur. The technics that have been developed for the use of the agent must be observed, and only experienced operators should employ the preparation. Asthmatics under treatment with acetylcysteine should be carefully supervised.

Acetylcysteine appears to be nonirritating, and no evidence of sensitization has been reported. Several cases of stomatitis, nausea, and occasional rhinorrhea have been described. Some subjects may note a slight disagreeable odor (sulfide-like). Susceptible asthmatics may experience some bronchospasm (as with any acrosol). The bronchospasm may be relieved by the use of a bronchodilator given by nebulization.

**Local medication in rhinitis and sinusitis.** Acute rhinitis is characterized by edema of the nasal mucosa, nasal discharge, and obstruction of the nasal passages. The condition usually results from viral or bacterial infection or as an allergic manifestation. Symptomatic relief is often achieved by the local use of a spray containing a sympathomimetic amine such as phenylephrine (Neosynephrine) or ephedrine. These agents act locally upon the nasal tissues through their sympathetic nerve supply, causing a shrinkage of both the surface (mucosal) vasculature and the turbinal cavernous spaces, thus reducing edema, shrinking the turbinates, and affording a more effective air passage for the patient. The ideal drug exerts the least effect upon the surface vessels and the greatest effect upon the erectile (cavernous) structures.

Dextro-pseudoephedrine (Sudafed) is a form of ephedrine that is considerably weaker as a pressor agent, yet it elicits about the same degree of bronchial dilatation and nasal vasoconstriction. Administered orally in 60-mg. doses to adults, this alkaloid, while requiring 30 to 60 minutes to produce its maximal effect, will relieve nasal congestion for prolonged periods.

Naphazoline (Privine) probably does not exert its action upon the same receptor sites as does epinephrine and the other adrenergic agents. Thus, in cases where preparations such as epinephrine, phenylephrine, or ephedrine have been employed for a considerable period of time with diminishing effects, naphazoline may be found to be effective in again shrinking the affected tissues. However, as the naphazoline medication is continued, it too soon fails to produce shrinkage as the tissues assume a state of near-paralysis from repeated stimulation without adequate recovery (chronic vasomotor rhinitis). In addition, naphazoline produces a disproportionately greater amount of vascular contraction in the mucosal vessels than the sympathomimetic amines; this leads to serious ischemia of the mucosal epithelium which often results in permanent pathologic changes.

Otrivin, an imidazoline vasoconstrictor, is said to produce fewer side effects and less rebound congestion than naphazoline. A 0.1 per cent solution of Otrivin is used for adults, and 0.05 per cent solution is recommended for children.

There are many types of decongestants for the nasal passages among the sympathomimetic amines. In a choice of one of these it is important to select an agent which does not irritate the affected membranes and which can be incorporated into a preparation which meets the criteria for rational therapy as previously outlined. In addition, it should not cause turgescence (rebound effect) or vasomotor imbalance upon repetitious application. For many years solution of phenylephrine hydrochloride has served admirably as a nasal decongestant without side effects; indeed, Solution Phenylephrine Hydrochloride, U.S.P. (Neosynephrine), in concentrations of 0.25 to 0.5 per cent, has become the standard by which other sympathomimetic agents are judged. The solution is also available containing 0.001 per cent of dioctyl sodium sulfosuccinate (Aerosol OT100) to reduce surface tension and thus promote penetrability. For prolonged contact with the nasal mucosa phenylephrine is also available as a "nasal jelly" in 0.5 per cent concentration. Some of the decongestants which have sufficiently high vapor pressure are available in the form of a nasal inhaler such as Benzedrex Inhaler.

**Epistaxis.** Epistaxis or nosebleed is a frequently encountered emergency. It may be entirely a local condition resulting from trauma, focal infection, or ulceration. On the other hand, the hemorrhage may be a local manifestation of a systemic disease such as scurvy, congestive heart failure, hypertension, rheumatic fever, various blood dyscrasias, or other disorders.

It is obvious that the cause of the epistaxis should be determined. The hemorrhage may often be checked effectively by simple measures. The area of bleeding, when located, may be cauterized with silver nitrate solution (page 207). Packing the nasal cavity with gauze tape moistened with epinephrine hydrochloride solution, 1:100, is usually effective in checking the hemorrhage.

### The Use of Drugs in the Treatment of Throat Affections

Drugs are frequently applied to the membranes of the throat and mouth by means of direct application of sprays, lozenges, or gargles. Mouth or throat lesions may represent a local manifestation of a systemic disease such as tuberculosis, diphtheria, syphilis, or one of the many blood dyscrasias. In the majority of instances cough is the result of acute infection of the upper respiratory passageways. Demulcents and expectorants used in throat affections are discussed in Chapters 15 and 19, antitussive drugs in Chapter 23. The clinical pharmacology of these drugs has been reviewed by Bickerman (1962).

**Pharyngitis.** Pharyngitis or sore throat is a condition usually caused by one of the pathogenic bacteria or the result of viral or allergic causes. The pharynx is inflamed, swollen, and tender. The patient complains of soreness especially on attempted swallowing, a tickling sensation in the throat, and often an annoying, nonproductive cough. There may be cervical adenopathy and high fever.

The local application of silver nitrate solution, 10 to 20 per cent, to specifically ulcerated or inflamed areas often affords great relief. Systemic medication with penicillin or one of the broad-spectrum antibiotics is also indicated. Many laryngologists favor *Mandl's solution* instead of silver nitrate for local application to the mucous membrane. This is a 2 per cent solution of iodine in glycerin containing 4 per cent potassium iodide flavored with oil of peppermint. It is very viscid in character and tends to adhere to the mucous membranes.

For palliative treatment lozenges are available containing such medicaments as local anesthetics, bacteriostatics, volatile oils, organic mercurial antiseptics, and antibiotics. Their chief merit is in relieving the annoying dryness and tickling of the throat that often accompanies pharyngitis. When infection is present in the crypts of the tonsils, the use of a medicated chewing gum serves the purpose of creating a mechanical action to squeeze the contents out of the crypts.

The use of gargles accomplishes little. In the act of gargling the fauces are completely closed, and the medicaments in the gargle do not reach beyond the anterior pillars of the throat, whereas the areas of infection are posterior to this region. It is far better to place such cleansing gargles in an atomizer and spray the throat with them. In this way some palliative effect can be attained.

**Laryngitis.** Acute or chronic inflammation of the larynx may occur with the common cold or sequentially after the acute nasal symptoms have disappeared. In addition, it may be a manifestation of a systemic disease. Hence, its origin should be determined. Hoarseness is the main symptom and may progress to complete aphonia. Dyspnea may be present if the larynx has become edematous. Coughing is an annoying symptom which is almost always present.

If the laryngitis is primary, bed rest, and the inhalation of water vapor with compound benzoin tincture is usually helpful. The use of elixir of terpin hydrate is beneficial in shortening the duration of the attack. If coughing is present, it may be controlled by 8- to 15-mg. doses of codeine. An atomized spray containing 1 per cent ephedrine sulfate or 1:10,000 epinephrine hydrochloride is often effective in relieving edema if applied to the larynx every 2 or 3 hours.

In pharyngitis or laryngitis the cough can usually be treated symptomatically with a demulcent syrup and an expectorant drug. A persisting, troublesome cough can be assuaged by one of the newer non-narcotic antitussives. Codeine may be reserved for the recalcitrant cough that requires sedation.

### The Use of Drugs in Ear Affections

Many types of drugs are used in the treatment of diseases encountered in the ear. Some of these are applied locally in diseases of the external and middle ears. Others, such as the antibiotics, are used systemically in the treatment of inflammation of the middle ear (otitis media). In the treatment of conditions affecting the internal ear (labyrinthitis), the antimotion sickness drugs and the antihistaminic agents are used.

**External ear.** The external ear is often the site of furunculosis, fungus infection (otomycosis), viral infection (herpes zoster), and dermatitis (eczema). Aural furunculosis is usually very painful and accompanied by swelling and even local adenopathy. Treatment consists of the application of packs, saturated with astringent or bacteriostatic agents, directly into the canals. The antibiotics in special ointment bases or combined in solution with a wetting agent to promote penetration are effective. Lidosporin otic solution is used for this purpose.

*Lidosporin otic solution* contains polymyxin B sulfate equivalent to 10,000 units in each milliliter with 5 per cent lidocaine hydrochloride in propylene glycol. The preparation is used in the treatment of infections associated with otitis externa, otitis media (if the tympanic membrane is perforated), otomycosis, and furunculosis. The local anesthetic acts to relieve the pain and itching associated with inflammation of the external and middle ear.

*Otamylon* is a bactericidal, fungicidal, analgesic solution containing 5 per cent sulfamylon hydrochloride and 5 per cent ethyl aminobenzoate in propylene glycol. It is instilled into the external ear canal after the ear has been cleansed and dried.

The most common fungus infections of the external ear canal are due to *Aspergillus niger, A. flavus, or A. fumigatus.* These occur frequently from swimming in contaminated water and the lack of aural hygiene. Since the fungi thrive in dark, moist, warm host tissues, it is important to cleanse the canals and thoroughly dry them. The use of 70 per cent alcohol and warm air insufflated into the canal usually accomplishes this drying efficiently.

Moist eczemas are treated by thorough cleansing and drying of the area. Astringent lotions with or without the addition of antihistaminics and/or corticosteroid agents usually provide relief from the annoying itching and allay the symptoms. In the dry scaly forms of dermatitis, soothing ointments containing antipruritic agents, antihistaminics, antiseptics, and corticosteroid agents may prove beneficial. Fabricant (1957) found the pH of the skin of the external auditory canal to be 7.1 to 7.8. It is believed that the instillation of an alkaline solution into the external auditory canal produces a state of alkalinity that is unphysiologic and enhances the infection. Slightly acid ear drops may encourage healing by providing an unfavorable environment for bacterial growth.

**Tympanic membrane.** Inflammation of the tympanic membrane may be caused by infection or trauma. It is referred to as *myringitis*. Irritants may gain access to the tympanic membrane, or pressure changes caused by diving or airplane descents may produce traumatic inflammation. The infectious types of myringitis often occur as a sequel to acute upper respiratory infections. Pain, impaired hearing, and generalized headache are common symptoms.

The pain in either instance may be controlled by aspirin and codeine, and by the local instillation of ear drops. When infected vesicles are present on the ear drum, it is preferable to employ a dehydrated glycerin ear drop containing an antibiotic to prevent spread of the infection and furunculosis of the canal. Systemic therapy with a broad-spectrum antibiotic or sulfonamides is often desirable in these cases.

**Eustachitis.** Inflammation of the Eustachian tube is almost always due to infection of the upper respiratory tract. A feeling of fullness in the ear, impaired hearing, tinnitus, and vertigo are common symptoms. Nasopharyngeal examination reveals congestion about the Eustachian orifices, mucoid or mucopurulent discharge in the nasopharynx, and the presence of edematous infected lymphoid tissue about the tubal lips in most cases.

Local relief is achieved usually by a nasal spray of a sympathomimetic amine such as phenylephrine (Neosynephrine) solution 0.5 per cent or ephedrine sulfate solution 1 per cent. Aspiration of the secretions from the nasopharynx is often helpful. During the acute stage of inflammation, the systemic use of antibiotics or sulfonamides is usually indicated to prevent complications such as otitis media.

**Acute otitis media.** Acute inflammation of the middle ear usually is a result of bacterial invasion from the nasopharynx by way of the Eustachian tube. Various common pathogens both bacterial and viral in character may be the infecting agents. Earache is the most common symptom. A feeling of fullness usually precedes the earache, and impaired hearing is always present. The primary cause of the disease almost always responds well to systemic sulfonamide, penicillin, or broad-spectrum antibiotic therapy. For the relief of symptoms while awaiting subsidence of the infection, warm Auralgan drops instilled in the ear canal every ½ to 1 hour usually afford much comfort. The antipyrine and benzocaine in this preparation serve as local analgesics, and the dehydrating action of the glycerin elicits a decongestant effect upon the tissues. Phenol in glycerin was formerly employed for this purpose but is less effective and even harmful because the phenol produces an escharosis of the ear drum with subsequent masking of the landmarks and delayed healing. Lidosporin otic solution is effective to relieve pain and itching. Aspirin and codeine are often necessary to control the pain.

**Chronic otitis media.** Persistence of infection in the middle ear may result in permanent perforation of the tympanic membrane and a chronic discharge. Unless the infection is checked the process may lead to serious mastoid involvement. It is imperative that water and aqueous solutions be kept out of the ear. The use of glycerin ear drops containing bacteriostatic agents is usually effective. When the discharge is malodorous from protein putrefaction, the addition of urea in combination with such medication is especially useful. Antibiotic ear drops are available in which polyethylene glycol has replaced glycerin as the hygroscopic base. This base has the advantage of a very much lower surface tension and hence more effective spreading than glycerin, thus enabling the antibiotic or antibacterial agent to reach all portions of the diseased middle ear. On the other hand, the glycol preparations have the decided disadvantage of stimulating granulations after repeated use. This is most undesirable, and the use of such glycol preparations is limited to a period of not more than 2 weeks. Careful observations should be made when glycol preparations are instilled in the ear, and the ear drops discontinued at the first signs of granulation formation. Glycerin preparations, on the other hand, are more hygroscopic and tend to inhibit granulation formation. The simultaneous use of systemic antibiotic therapy is often most valuable in chronic otitis media.

**Labyrinthitis.** Inflammation of the internal ear (labyrinth) is usually spoken of as *Ménière's syndrome*. The acute episodes are most distressing to the patient and often disabling. Bed rest in a darkened room often provides relief of symptoms of vertigo, nausea, and vomiting. Formerly, restrictions were placed upon the salt (sodium) intake of these patients, and enteric-coated tablets of potassium chloride in doses of 1.0 to 2.0 gm. 3 or 4 times a day are still widely used. Dimenhydrinate (Dramamine), parenterally and orally, often provides dramatic relief. In some patients meclizine (Bonine) is more effective.

### THE USE OF DRUGS IN THE EYE

Many drugs are used in the treatment of the great variety of local eye affections. As in the case of the ear, nose, and throat, the therapy may be systemic or applied locally by the instillation of the medicament into the conjunctival sac. The local use of drugs in the eye is the principal concern of this discussion. The use of homatropine for refraction is discussed on page 605. Physostigmine in glaucoma is considered on page 583, and many other references in this treatise deal with the effects of drugs on the eye systemically or locally.

A remarkable development in the treatment of the viral disease, herpes simplex keratitis, is the drug idoxuridine; the first agent to cure a true viral disease. Idoxuridine is discussed as a specific drug in the cure of this viral infection.

Levo epinephrine bitartrate has been found to be effective when applied locally in the treatment of chronic simple glaucoma. The action of the sympathomimetics on the eye is discussed in Chapter 34. The use of epinephrine solutions in the treatment of wide angle glaucoma is mentioned in this section. The exact mechanism of action is not known. It is believed that the sympathomimetic amine inhibits the formation of aqueous humor.

A 1 or 2 per cent solution of levo epinephrine is instilled twice daily. The result is a decrease in intraocular tension within 1 hour, and the effect lasts for approximately 24 hours. The drug is often used in combination with pilocarpine solution or other miotics and/or carbonic anhydrase inhibitors.

**The conjunctiva and the tear.** The surfaces of the conjunctiva are lubricated and cleansed by a film of tear fluid secreted by the lacrymal glands. The tear secretion contains 98.2 per cent of water and 1.8 per cent of total solids. There are traces of albumin, globulin, and urea in the tear as organic solutes. The principal inorganic solute is sodium chloride which is present to the extent of about 0.7 per cent. The pH of the tear from normal eyes closely approximates that of blood, 7.2 to 7.4. The values recorded in various disease conditions vary from pH 5.2 to 8.3. The most effective medications for instillation into the conjunctival sac are those which are adjusted to a pH approximating that of the normal tear and are also nearly isotonic with the tear secretion.

Boric acid has been used for many years, in the form of a saturated solution, for treating conjunctivitis, blepharitis, and minor eye irritations. The substance has very little value as an antiseptic, and, indeed, ophthalmic solutions of the drug must be boiled to render them sterile. Boric acid is toxic if improperly administered and its use should be discouraged (see page 216). Ophthalmic solutions for medicinal or cosmetic purposes, *e.g.*, contact-lens solutions, must be sterile according to the Food and Drug Administration regulations.

**Blepharitis.** This condition is an inflammation of the margins of the eyelids. It is usually due to bacterial infection or response to an allergen. The infection is usually staphylococcic or caused by the Morax-Axenfeld diplobacillus and the Koch-Weeks bacillus. Streptococci or pneumococci are less frequently involved. Avitaminosis may be a contributing factor. The lid margins become red and edematous, and the lid surface presents a glossy appearance. The cause of the condition should be determined if possible.

Blepharitis responds best to simultaneous local and systemic treatments. Locally, penicillin ointment is helpful because the infection, if present, is frequently staphylococcic. Penicillin, the broad-spectrum antibiotics or sulfonamide therapy may be used systemically. In refractory cases the lid margins may be painted with 0.5 per cent silver nitrate solution. If the condition is allergic, antihistaminic therapy is indicated systemically. An antihistaminic agent may also be used locally in ointment form. However, for the local therapy fluorohydrocortisone ointment (see page 838) is usually more effective.

Several times daily the instillation of a few drops of a collyrium containing phenylephrine hydrochloride and zinc sulfate is most helpful.

Zinc sulfate is one of the most useful astringent drugs available for treatment of local inflammatory conditions of the eyelids and conjunctiva. If the causal agent is the diplobacillus of Morax-Axenfeld, a 0.5 to 1 per cent zinc sulfate solution is specific in relieving the infection. It is thought that the bacteria produce an enzyme which has an affinity for the skin; this accounts for the distribution of the lesion to the outer 2 to 4 mm. of the lid margins.

**Hordeolum.** Hordeolum or stye is an acute localized infection of one or more of the glands of Zeiss or Moll (external stye) or of the meibomian glands (internal stye). This is generally a staphylococcic infection resulting from lowered bodily resistance, eye strain, or a blepharitis.

Hot compresses will usually hasten the suppuration. Systemic penicillin or sulfonamide therapy may be indicated. Erythromycin often proves specific. Local treatment is similar to that set forth under infectious blepharitis.

**Conjunctivitis.** This condition usually presents itself as a catarrhal form of acute inflammation of the conjunctiva and is the result of bacterial infection. The contagious epidemic form of conjunctivitis occurring often in the spring and autumn (pink eye) is usually caused by pneumococci. Burning sensation, lacrimation, itching, and photophobia are symptoms frequently encountered.

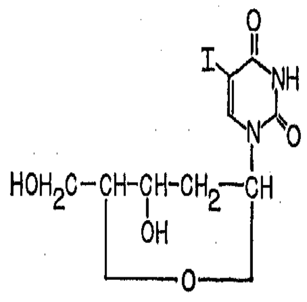
This type of conjunctivitis as a rule is self-limiting. The treatment consists of protection of the eyes from light, cold compresses, and the local application of penicillin ointment. If the conjunctivitis persists, systemic therapy with penicillin, the broad-spectrum antibiotics, or sulfonamides may be necessary.

Menger (1959) found tetrahydrozaline (Tyzine), 2-(1,2,3,4-tetrahydro 1-naphthyl) imidazoline hydrochloride, useful as a vasoconstrictor when employed in a 0.05 per cent solution by instillation in the eye. The preparation is known as Visine. Ophthalmic drops provided effective decongestant action in allergic conjunctivitis and in various forms of chronic conjunctivitis. The solution did not raise the intraocular pressure and had no adverse effects when used for as long as 2 years in patients with cataracts. The desired relief was obtained in the majority of patients, and side effects of mild transient irritation were the only undesirable reactions.

**Herpes simplex keratitis.** This is a viral disease of the eye characterized by many manifestations. It is exhibited first as a superficial infection of the eye by minute epithelial opacities which may be followed by vesiculation and necrosis. The typical picture is a dendritic ulcer. The scarring and vascularization produced, especially by recurrent attacks, can cause severe visual impairment. Sharp pain in the eye may be experienced, and a haze of fine, granular white spots in the epithelium may result. The spots and fissures that are formed are stained by fluorescein dye. With recurrent attacks, deeper penetration of the cornea takes place involving the stroma and eventually the corneal endothelium. This latter stage is described as deep keratitis.

Herpes simplex is a virus of the desoxyribonucleic acid (DNA) type. Viral infection in a cell causes a marked increase in the DNA content of the cell. The concept of Kaufman that a compound which would inhibit viral DNA synthesis might be effective against herpes simplex keratitis, led the way to the discovery of 5-iodo-2′-deoxyuridine (Kaufman, *et al.*, 1962).

**Idoxuridine (Stoxil, Dendrid, Herplex).** Idoxuridine is an analog of thymidine, a substance required for the synthesis of DNA. In idoxuridine an iodine atom replaces a $CH_3$ group in thymidine. It is 5-iodo-2′-deoxyuridine.



Idoxuridine

It is assumed that idoxuridine is taken up by the developing virus in place of the essential thymidine. This deprives the virus of its required metabolite that is necessary for viral reproduction. Idoxuridine may be considered to be active as an antimetabolite. When administered systemically, untoward effects limit the use of idoxuridine. However, topical administration to the relatively avascular cornea permits the drug to be used as an antiviral agent locally.

An ophthalmic solution of 0.1 per cent idoxuridine is employed in the treatment of herpes simplex keratitis by instilling one drop in each infected eye every hour during the day and every 2 hours at night. This dosage is continued until definite improvement has taken place, as demon-

strated by loss of the staining of the dendritic ulcer by fluorescein. Normally the duration of treatment should not exceed 21 days.

Idoxuridine is indicated in the treatment of herpes simplex keratitis, especially the epithelial infections associated with the initial attacks. Infections located in the stroma have shown a less favorable response. In recurrent cases the drug may control the current episode of viral infection, but old scars will not be removed. The best results with the antiviral agent are obtained in the treatment of superficial infections. Deep infections may respond, however. Complete healing often takes place after 1 or 2 weeks of therapy.

The side effects associated with the use of idoxuridine are not serious. Occasionally, irritation, pain, pruritus, inflammation, or edema will be experienced in the eye or lids. Allergic reactions and photophobia can occur. The solution of idoxuridine should not be administered more frequently than once an hour during the day and once every 2 hours at night because the development of punctate lesions on the corneal epithelium would be encouraged. More frequent administration will not improve the efficacy of the drug.

Perhaps the most significant aspect of the discovery of the effectiveness of idoxuridine in herpes simplex keratitis is that it represents a pioneering achievement in antiviral chemotherapy. Certainly the simplicity and rapidity of cure of this viral disease is noteworthy and bespeaks the possibility of the discovery of other effective antiviral drugs.

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# 19

# *The Response of the Gastrointestinal Tract to Drugs*

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Deglutition involves the reflex associations of the upper portions of the esophagus, the pharynx, the larynx, and the glottis. Saliva and the buccopharyngeal mucous secretions serve to facilitate the passage of food into the lower esophagus and stomach. The secretions of the mucosal cells of the respiratory tract bathe the respiratory passages and normally are gradually drained or moved by ciliary activity from the airway. These involved, mechanical processes are partially under voluntary control and are partly natural reflex. An appreciation of the physiology of these intricately related functions provides a better understanding of the role of drug therapy in nausea, vomiting, coughing, and pharyngeal and laryngeal irritations. These physiologic mechanisms play a significant role in the mechanism of action of expectorants and the antiemetic agents.

## EXPECTORANTS

*Drugs which augment the secretion of respiratory tract fluid and facilitate its expulsion are termed expectorants.* When irritation of the mucosa below the epiglottis occurs, a dry, nonproductive, hacking cough is produced. If the source of irritation is not removed by the cough reflex, a persisting tussal hyperreflexia results. This type of cough is difficult to treat. The cough reflex originating in the pharynx may be soothed by demulcent throat lozenges or cough syrup. On the other hand, the cough reflex originating in the mucosa of the larynx, the trachea, or the respiratory tree is very difficult to assuage. In the latter case expectorants, which encourage the outflow of the natural demulcent respiratory tract fluids, may be most helpful. Expectorants permit the dissolution of the irritant or facilitate its removal via the upward streaming of an increased volume of respiratory tract fluid. The copious mucous fluid is coughed out of the respiratory tract and expectorated.

Expectorants can exert their effect in a number of ways. The secretions of the acinar glands of the respiratory tract are augmented by vagal stimulation and parasympathomimetic agents. However, these drugs are not suitable as simple expectorants. As a result of the recent experimental studies of Borison and Wang (1953) and others, the physiology of the reflex mechanisms existing between local gastric irritation, central medullary stimulation and salivation, nausea, and vomiting are better understood. Apparently, secretions of the respiratory tract are also influenced by these reflex functions. The expectorant qualities of the

emetic drugs, ipecac and apomorphine, have been recognized for many years. Emetic drugs in proper doses may elicit subthreshold stimulation of the chemoreceptor trigger zone in the medulla. The vomiting center is not activated, and emesis does not result, but the secretory reflex for salivation and increased respiratory tract fluid is intensified. There results a typical expectorant action. Inorganic salts such as ammonium chloride and sodium iodide are believed to exert their expectorant action by stimulating a reflex mechanism originating in the mucosa of the stomach. Irritation of the gastric mucosa has been shown experimentally to elicit increased secretion of respiratory tract fluid.

Technics for evaluating cough suppression have been developed for use in patients treated with expectorants and antitussive drugs (Woolf and Rosenberg, 1963). The value of mucolytic agents in treating cough with cough suppressives and expectorants, has been studied (Webb, 1962). Mucolytic agents liquefy the viscid bronchial secretions in a manner resembling the action of expectorants; their mechanism of action depends upon proteolysis and detergency. These agents, *e.g.,* N-acetyl-L-cysteine, at present are used experimentally and are administered by nebulization or direct tracheal installation.

**Ammonium Chloride, U.S.P.** (NH$_4$Cl), is a colorless crystalline powder. It has a cool saline taste. One gram of ammonium chloride dissolves in 2.6 ml. of water. The usual expectorant dose is 0.2 gm. As an expectorant, ammonium chloride is usually prescribed in a cough syrup. The demulcent action of the syrup is desirable and tends to allay the associated cough and pharyngeal irritation. Large doses irritate the stomach and may cause nausea and vomiting. Enteric-coated capsules or tablets are used when large doses of ammonium chloride are administered as a diuretic, page 811.

**Potassium Iodide, U.S.P., and Sodium Iodide, U.S.P.,** are colorless crystalline powders. One gram of potassium iodide dissolves in 0.7 ml. of water, 1 gm. of sodium iodide in 0.6 ml. of water. The expectorant dose of either of these salts is 0.3 gm. Sensitivity of certain individuals to iodides occasionally limits the use of these salts as expectorants.

## THE GASTRIC ANTACIDS

Gastric antacids are substances employed to diminish the quantity of hydrochloric acid in the stomach. They accomplish this by 3 different mechanisms. The first is by direct neutralization. Examples of compounds in this class are sodium bicarbonate and magnesium oxide. The second mechanism is a buffering of the gastric acid, normally pH 1 to 2, to a lower hydrogen-ion concentration. Examples of this class are sodium citrate and magnesium trisilicate. The third mechanism combines adsorption of the hydrogen ions of hydrochloric acid, buffering, and partial neutralization of the acid. Substances in this class are hydrated aluminum oxide and anion exchange resins. Each mechanism in the counteracting of excessive gastric acidity has its specific advantages.

Gastric antacids constitute one of the largest groups of medicinal substances employed in medical practice and by the laity. They are used specifically in the treatment of gastric hyperacidity and "peptic ulcer." Gastric hyperacidity gives rise to symptoms of fullness after eating, gastric distension, eructation, and heartburn. Frequently, the simple reduction of the hydrochloric acid content of the stomach by any of the foregoing mechanisms will provide relief. The term "peptic ulcer" is used to designate a localized destruction in the mucosa of the gastrointestinal tract which is bathed by the gastric juice. Hence, it includes gastric and duodenal ulcers which are believed to be caused by an imbalance of the reciprocating autonomic nerve supply of the stomach and duodenum. This results in a diminished supply of blood to areas of the mucosa bathed with a gastric juice rich in hydrochloric acid and pepsin. Erosion and frank ulceration occur, which may proceed through the muscular walls of the intestine, producing perforation. The healing of the ulcer is dependent upon the neutralization or buffering of the acid for long periods, along with other therapeutic measures, such as rest, bland diet, antispasmodic drugs, and sedatives.

Gastric antacids may be divided into 2 classes with respect to their therapeutic use. These classes are the *systemic antacids* or *alkalotic agents* and the *local antacids.* The first class of compounds is readily absorbed from the gastrointestinal tract. Sodium bicarbonate, sodium citrate, and sodium acetate are typical members of this class. The absorption of the sodium ion augments the alkaline reserve of the blood. The power of the blood to combine with carbon dioxide is materially augmented. If systemic antacids are used excessively, an alkalosis follows which is characterized by headache, abdominal pain, nausea, and vomiting. The second class of antacids contains cations which are poorly absorbed; hence, these compounds have no direct effect upon the acid-base equilibrium of the blood. Examples of this class are magnesium oxide, calcium carbonate, and aluminum hydroxide gel.

**Sodium Bicarbonate, U.S.P.** ($NaHCO_3$). Sodium bicarbonate is a white, crystalline powder. It is soluble in 10 parts of water at 25°C.; hot water decomposes it. A 0.1 M solution of sodium bicarbonate exhibits a pH of 8.3. As an antacid it is administered dissolved in water or compressed in tablets. The average dose is 1 gm. This quantity will neutralize approximately 120 ml. of 0.1 N hydrochloric acid. It is unable to produce a prolonged buffering effect, and further, frequently produces gastric distention through the liberation of carbon dioxide. The compound has the capacity of alkalinizing the stomach to pH 8.3 and thus definitely inactivating pepsin; this can be undesirable. In addition, clinical investigators hold the view that alkalinizing the stomach with a substance like sodium bicarbonate may cause the subsequent secretion of an excess of hydrochloric acid, so-called "acid rebound." When the stomach is devoid of hydrochloric acid, the ingested sodium bicarbonate is absorbed unneutralized, and the alkali reserve of the blood is augmented.

**Magnesium Oxide, U.S.P.** (MgO). Magnesium oxide is a fluffy, white, insoluble powder. It reacts slowly with hydrochloric acid.

The compound is administered in powdered form. The dose is 0.25 gm.; in larger doses, such as 3 gm., magnesium oxide produces catharsis. One gram of magnesium oxide will neutralize approximately 500 ml. of 0.1 N hydrochloric acid. The magnesium ion is poorly absorbed from the gastrointestinal tract; therefore, magnesium oxide falls in the category of local-acting antacids.

**Magnesia Magma, U.S.P.** This preparation is an aqueous suspension of magnesium hydroxide [$Mg(OH)_2$] containing approximately 8 per cent of the base. The pH of the aqueous suspension is approximately 10.6; it possesses a large reserve acid-consuming capacity. The mechanism of its action is similar to that described under magnesium oxide. The dose of the magma as an antacid is 4 ml., as a laxative 15 ml.; 10 ml. of magnesia magma will neutralize approximately 270 ml. of 0.1 N hydrochloric acid.

**Magnesium Trisilicate, U.S.P.** Magnesium trisilicate or metasilicate has the approximate composition $Mg_2Si_3O_8 \cdot nH_2O$ or $2MgO \cdot 3SiO_2 \cdot nH_2O$. It is not a native magnesium silicate but is prepared by slowly adding aqueous solutions of various sodium silicates to aqueous solutions of magnesium sulfate. The resulting precipitate is washed free of sulfate. Magnesium trisilicate is a fine, white, odorless, tasteless powder free from grittiness. It is insoluble in water but is readily decomposed by mineral acids. It is administered as a powder or as tablets. The compound reacts slowly with hydrochloric acid.

The dose of magnesium trisilicate is 1 gm.; this quantity neutralizes approximately 102 ml. of 0.1 N hydrochloric acid. Magnesium trisilicate is an example of a local-acting antacid. The compound becomes gelatinous in the presence of gastric juice, because of the formation of hydrated silicon dioxide. This latter substance serves as an adsorbent for toxins and is said to be valuable in coating the crater of ulcers, thus protecting the irritated mucosa from the digestive action of pepsin and hydrochloric acid. Magnesium trisilicate is extensively used to provide a prolonged diminution of gastric acidity.

**Precipitated Calcium Carbonate, U.S.P.** ($CaCO_3$). Precipitated calcium carbonate used for medicinal purposes is a white, microcrystalline powder. It is very sparingly-soluble in water. Calcium carbonate reacts slowly with the hydrochloric acid in the stomach.

The compound is usually administered in the form of a powder or discoid wafers, in a dose of 1 gm. This quantity of calcium carbonate will neutralize approximately 200 ml. of 0.1 N hydrochloric acid. Calcium carbonate is a nonsystemic antacid. After neutralization, the resulting calcium chloride remains for the most part unabsorbed and is excreted in the feces.

**Aluminum Hydroxide Gel, U.S.P.** As used medicinally, aluminum hydroxide gel is a hydrated form of aluminum oxide, yielding upon ignition not less than 50 per cent of $Al_2O_3$. The dried gel is a white, odorless, tasteless, amorphous powder. It is insoluble in water but soluble in dilute solutions of mineral acids and fixed alkalies. The substance is administered as discoid tablets, or as an aqueous suspension of 3.6 to 4.4 per cent of the hydrated oxide. The dose of dry, hydrated aluminum oxide is about 0.6 gm. The U.S.P. requires that each gram of the gel shall consume not less than 12.5 and not more than 25 ml. of 0.1 N hydrochloric acid at 37.5°C. The aluminum hydroxide gel partially neutralizes and partially adsorbs the gastric acid. It does not produce an alkaline reaction and hence does not produce the so-called "acid rebound." This antacid has a prolonged buffering effect on gastric acid, but as with magnesium trisilicate, the onset of action is usually slow. The compound may produce constipation in certain individuals. It is a nonsystemic antacid.

Aluminum hydroxide gel, when administered in large doses such as 60 to 100 ml. daily, markedly diminishes the absorption of phosphate. Hence, the phosphate excreted in the urine is reduced. Use is made of this action to inhibit urinary concretions of the calcium phosphate type.

Local anesthetics, *e.g.*, oxethazaine (Oxaine), have been added to aluminum hydroxide gel to provide a topical anesthetic action on the inflamed gastric mucosa of patients suffering from chronic gastritis and chronic esophagitis. For many years the local anesthetic drugs have been used in treating peptic ulcer in an attempt to allay the pain. However, the value of these drugs in treating this condition has not been established.

**Dihydroxyaluminum Aminoacetate, N.F. (Alglyn, Alzinox, Dimothyn, Robalate).** This antacid is a white, impalpable powder with a bland taste. It is insoluble in water, but mixes easily with water to form suspensions which do not readily separate. In aqueous suspension (1 in 25) at 25°C. it exhibits a pH of 7.4. This compound is administered in tablet form. The dosage is 0.5 to 1 gm.; the latter quantity of this substance will buffer approximately 200 ml. of 0.1 N hydrochloric acid to pH 4 at 37.5°C. in 1 hour. Aluminum dihydroxyaminoacetate gives immediate and prolonged neutralization of gastric acidity.

**Aluminum Phosphate Gel, N.F.,** is a 4 per cent water suspension of $AlPO_4$. Its antacid and astringent properties are analogous to those of aluminum hydroxide gel, but it does not interfere with phosphate absorption. The dose is 8 ml. The acid-combining power of aluminum phosphate gel is less than one-half that of aluminum hydroxide gel of the same concentration; usual doses are therefore twice as great.

**Basic Aluminium Carbonate (Phosphaljel).** This preparation is an aluminium hydroxide-carbonate complex available as a white, creamy, thixotropic gel. It is an aqueous suspension containing the equivalent of 4.9 to 5.3 per cent aluminium oxide and 2.4 per cent carbon dioxide. It exhibits a pH range of 6.6 to 7.0.

Basic aluminium carbonate combines with the phosphate ion in the intestinal tract in a manner similar to aluminium hydroxide. It is about one-third more effective than the latter substance in phosphate-binding power. Therefore, it is the superior product to use in reducing the concentration of urinary phosphate in patients susceptible to the formation of phosphatic calculi of the urinary tract. Basic aluminium carbonate shares the antacid properties of the related aluminium preparations.

**Tribasic Calcium Phosphate, N.F.** ($Ca_3(PO_4)_2$), is a white, odorless, tasteless powder insoluble in water. As an antacid this insoluble compound produces less systemic alkalinization than sodium bicarbonate. The dose is 1 gm.

**Tribasic Magnesium Phosphate, N.F.** ($Mg_3(PO_4)_2$), is a white, odorless, tasteless, insoluble powder. Its action and uses are the same as tribasic calcium phosphate. The dose is 1 gm.

**Anion Exchange Resin (Resinat, Exorbin).** Naturally-occurring silicates, such as zeolites, and certain synthetic "artificial zeolites" have been used as water softeners for many years. These substances are capable of removing calcium and magnesium ions from water and thereby decreasing its hardness. These cations are replaced by sodium ions, and the materials thus became known as *ion exchangers*. The discovery that ion exchange properties are possessed by synthetic resins led to the development of a new type of exchange adsorbent, the *anion exchange resins*. These substances remove acids from solution by direct *adsorption*. A medicinal form of this type of resin is the substance employed therapeutically as an antacid. The resin is described as a polyethylene polyamine methylene substituted resin of diphenylol dimethyl methane and formaldehyde in basic form. The substance is a water-insoluble powder ground to a 200-mesh particle size. It acts as an acid adsorbent and is said to be eliminated without change in its chemical composition. The resin is essentially nontoxic, but large doses may produce nausea or vomiting.

The resin is available in capsule and tablet form. The dosage in peptic ulcer therapy is 0.5 gm. at hourly intervals daily for 1 week, then 0.5 gm. every 2 to 3 hours while the patient is awake.

**Choice of an antacid.** There have been many attempts to evaluate the efficacy of the generally used antacids. In addition to effectiveness in the adsorbing, buffering, and neutralizing of gastric acidity, there are other factors of prime importance. Among these the following are considered as essential criteria:

1. Prolonged acceptance by the patient.
2. Freedom from toxic or other untoward effects.
3. Action confined to the alimentary tract.
4. Absence of constipative action.
5. Immediate and prolonged neutralization of acid without producing gastric contents with an acidity above pH 4.

In the main, these properties are common to aluminum dihydroxyaminoacetate, aluminum hydroxide gel, and magnesium trisilicate.

The U.S.P. test for the acid-consuming capacity of aluminum hydroxide gel does not take into account the *time* required for acid neutralization. The rapidity of neutralization, as well as how long an antacid is effective, are both important therapeutic considerations and should be evaluated. Holbert and his associates (1948), Hammarlund and Rising (1949), and Dale and Booth (1955) have made comparative studies of antacid buffers. In general they have found that an artificial gastric juice *in vitro* is neutralized most promptly and for long periods by dihydroxy-aluminum aminoacetate and some commercial preparations of aluminum hydroxide gel. Some antacids act very slowly to neutralize the acidity, and if employed in excess, an initial pH rise considerably above pH 4 may be obtained. Magnesium trisilicate antacids are rapid-acting, but their sustaining action is weak. Mixtures of 2 parts of aluminum hydroxide and 1 part of magnesium trisilicate seem to combine the best features of each of these agents.

*In vitro* measurement of neutralization does not reproduce the secretory potential of the human stomach; therefore, antacid evaluation is best determined directly in the ulcer patient under well-controlled conditions. Lehman and Pollack (1955) stress that the antacid must be administered in an adequate dose because no benefit is produced until peptic activity is suppressed, and this requires about 90 per cent neutralization of the acid present in the stomach. They found liquid preparations of aluminum hydroxide and magnesium hydroxide superior to tablets of the same compounds. The aqueous suspension of the hydrated gels react more rapidly than the partially dehydrated, large particle size gels originating from tablet disintegration.

Packman *et al.* (1956) conducted a comparative study of antacids *in vitro* and *in vivo* in dogs with experimentally produced gastric fistulas. They reported that in a dose range of 0.5 to 1 gm. the antacids, in order of their decreasing effectiveness, were: dihydroxyaluminum sodium carbonate, aluminum hydroxide, calcium carbonate, and sodium bicarbonate. In their *in vivo* experiments over a 75-minute observation period only dihydroxyaluminum sodium carbonate maintained the gastric pH in the range of 3 to 5. They stress the advantage of the *in vivo* study over the *in vitro* procedure for evaluating antacids.

Brody and Bachrach (1959) have compared the chemical, physical, and therapeutic properties of the numerous antacids. They have evaluated these drugs on the basis of their *in vitro* acid-combining capacity and their cost to the patient. The many commercial forms were assayed, and it was found that products of similar chemical composition vary in their neutralizing capacity. Liquid preparations were more efficient than tablets. These workers found calcium carbonate the least expensive, effective neutralizer and the antacid of choice, if care is taken to prevent constipation. The possibility of alkalosis, depressed renal function, or development of renal lithiasis is admitted.

Bleifer *et al.* (1959) have measured the sodium content of various aluminum hydroxide and magnesium trisilicate preparations. Patients on a low-sodium diet may augment their sodium intake appreciably by taking these antacids. For these persons magnesium hydroxide, dihydroxyaluminum aminoacetate or calcium carbonate may be most satisfactory.

### ANTIEMETIC AGENTS

Nausea and vomiting are frequently serious therapeutic problems. Persistent nausea is a distressing state that interferes with proper food intake and results in an inadequate diet. Repeated vomiting is dangerous and can lead to serious consequences if not adequately controlled. It is capable not only of upsetting the electrolyte balance, creating dehydration, and exhausting the patient, but also may lead to the aspiration of vomitus into the lungs or a gastric hemorrhage. Nausea and vomiting may be symptoms of disease or they may follow the therapeutic use of drugs.

Numerous attempts have been made to control these symptoms, and recently, specific antiemetic agents have been discovered. Nausea and vomiting may be caused by stimuli arising in some part of the gastrointestinal tract or by stimulation of the chemoreceptor trigger zone for emesis in the medulla. Therapy directed at each of these sites is effective. The central nervous system depressants that are useful in the treatment of nausea and vomiting of motion sickness are discussed in Chapter 30. The antiemetic drugs have been studied intensively and used most effectively in postoperative nausea and vomiting. For this purpose they are injected parenterally.

Controlled double-blind studies of the effectiveness of these agents administered orally are rare. The numerous psychic factors associated with nausea and vomiting make the evaluation of an antiemetic drug difficult. However, controlled evaluative studies have been made (Blatchford, 1961).

Most of the antihistaminic agents discussed in Chapter 58 elicit some degree of sedation when they are taken in the usual oral doses. This sedative property seems to be related to antiemetic effectiveness, for these drugs have been used in the control of nausea and vomiting. Many of the tranquilizer phenothiazine derivatives are antihistaminics and in addition have pronounced sedative effects. Some phenothiazine drugs appear to inhibit the medullary emetic centers specifically without producing drowsiness.

A controlled double-blind study of prochlorperazine (Compazine), thiopropazate (Dartal), pipamazine (Mornidine), cinnarizine (Mitronal), and trimethobenzamide (Tigan) by Moertel *et al.* (1963), using a lactose placebo, revealed that the phenothiazines exerted a superior antiemetic effect. In this study, fluorouracil, a known emetic agent, was administered in the treatment of advanced carcinoma of the gastrointestinal tract. Thiopropazate and prochlorperazine were most effective. Pipamazine and cinnarizine exhibited a lesser degree of antiemetic activity, while trimethobenzamide showed only a slight advantage over treatment with the placebo. Nausea and vomiting resulting from disease might be considered in a different category of therapy. In these conditions drugs may or may not be effective therapeutic agents.

Representative phenothiazine drugs useful as antiemetics are discussed in this section; other members of this class are considered in Chapter 32.

**Chlorpromazine, U.S.P. (Thorazine).** Chlorpromazine was originally studied as an antihistaminic and sedative drug. It was found that when chlorpromazine was administered either orally or intramuscularly to dogs it would effectively inhibit apomorphine-induced vomiting. Subsequent studies in patients demonstrated that this drug was useful to control nausea and vomiting from various causes; uremia, pregnancy, cancer, irradiation, and gastrointestinal disease. Chlorpromazine is also beneficial in the control of hiccough. Its role in the treatment of psychiatric states is discussed in Chapter 32.

Most of the phenothiazine drugs have antiemetic properties; prochlorperazine (Compazine) and promethazine (Phenergan), in addition to chlorpromazine, especially have been used in this manner. In this section chlorpromazine is considered as representative of the class.

Dosage schedules with chlorpromazine as an antiemetic have been variable. Adult patients have been given 10-, 25-, or 50-mg. doses by either oral or the intramuscular route. The dose is repeated at varying intervals as frequently as necessary in order to control the symptoms. Initial doses may be given intramuscularly to bring the vomiting under control. Subsequent doses are by mouth usually 3 or 4 times a day. One of the most effective ways chlorpromazine has been used is in suppository form for children. The most important side effect is drowsiness, and this is considered beneficial in most cases. Dizziness, weakness, and faintness are overcome by having the patient remain recumbent, especially after parenteral injections. More severe toxic reactions have been encountered after chlorpromazine administration (see page 504).

In studies on experimental animals it has been shown that chlorpromazine apparently acts centrally to depress the medullary chemoreceptor emetic trigger zone. It is not very effective against locally-acting emetics that irritate the gastric mucosa, *e.g.*, copper sulfate. Presumably, all the phenothiazine derivatives that exhibit antiemetic properties have a similar mechanism of action.

**Pipamazine (Mornidine).** Pipamazine is a phenothiazine which is reported to be less likely to produce drowsiness than other chemically related antiemetic drugs. Pipamazine is 10-[3-(4-carbamoylpiperidino)-propyl]-2-chlorphenothiazine. The substance is off-white in color and dissolves readily in water.

Pipamazine has been used to prevent and control nausea and vomiting associated with pregnancy, radiotherapy, nitrogen mustard therapy, and other forms of drug therapy, gastroenteritis, and postoperative nausea and vomiting. The drug has relatively weak tranquilizing or sedative effects. Like the related phenothiazines it has a selective action on the chemoreceptor emetic trigger zone of the medulla.

The adult dose is one 5-mg. tablet every 4 to 6 hours. The same single dose may be administered intramuscularly. The drug should be administered with caution to patients also receiving barbiturates, narcotics, or other central nervous system depressants. As is the case with other phenothiazine derivatives, pipamazine may cause orthostatic hypotension in some patients, especially after large doses. The usual precautions of hematologic and hepatic tests are indicated when this drug is prescribed for patients for prolonged periods of time.

**Thiethylperazine Maleate (Torecan).** Thiethylperazine maleate is 2-ethylmercapto-10-[3-(1-methyl-4-piperazinyl)propyl] phenothiazine dimaleate. It is an antiemetic drug with less sedative activity than most of the other phenothiazine derivatives. It has been used to treat nausea and vomiting associated with the administration of general anesthetics. Its value in treating or preventing nausea and vomiting associated with other medical conditions remains to be established.

Thiethylperazine maleate is administered intramuscularly, orally, or rectally. The usual adult dose ranges from 10 to 30 mg. per day. The drug is available as a 10 mg. per 2 ml. solution for injection, 10-mg. suppositories, and 10-mg. tablets.

**Trimethobenzamide (Tigan).** Trimethobenzamide is a substituted benzamide that appears to have specific antiemetic and antinauseant properties. The substance in the form of the hydrochloride is a white crystalline, water soluble, bitter tasting powder. Chemically, it is 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine.

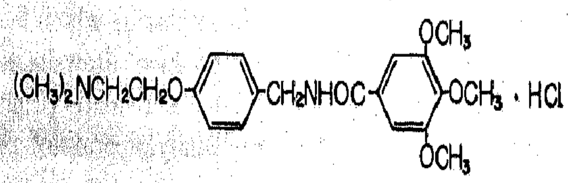
The antiemetic effectiveness of this drug apparently is related to its action on the chemoreceptor trigger zone. Trimethobenzamide will inhibit apomorphine-induced vomiting in dogs. It provides only partial protection from orally administered copper sulfate emesis in this species. Since copper sulfate produced emesis reflexly and independently of the chemoreceptor trigger zone, it is believed that trimethobenzamide will block emetic stimuli mediated by way of this medullary area but not visceral impulses to the vomiting center *per se.* The drug produces very little sedation and hence differs from the antiemetic agents that elicit marked central nervous system depression and drowsiness as a part of their antiemetic effects.

A number of uncontrolled clinical trials of trimethobenzamide have indicated its effectiveness in nausea and vomiting in pregnancy, radiation therapy, gastrointestinal infections, carcinomatosis, motion sickness, and nausea following drug therapy. Not all patients were benefited, but 75 per cent or more experienced complete or moderate relief.

The adult dose of trimethobenzamide is 1 to 3 100-mg. capsules administered 4 times daily. The dose is adjusted according to the severity of symptoms and the response of the patient. Children under 90 pounds should receive half the adult dose or less. Ampules are available containing 100 mg./ml. for parenteral therapy. The intramuscular adult dose is the same as the oral dose.

Relief of nausea and vomiting usually occurs within 20 to 30 minutes after oral doses. The effects of the drug last approximately 2 to 3 hours. In some patients relief is afforded for an entire day or night after a single dose.

Trimethobenzamide apparently does not elicit serious adverse side effects. Drowsiness may be produced but cardiovascular effects or skin rash have not been reported. No abnormal laboratory findings have been observed in patients on trimethobenzamide therapy for a period of several weeks. Because the drug does not cause sedation, it may be the agent of choice for ambulatory patients. Persons required to exercise motor skills and subject to motion sickness during automobile driving or flying should be candidates for therapy with this drug.



Trimethobenzamide, Tigan

**Phosphorated Carbohydrate Solution (Emetrol).** This preparation is a solution of levulose and dextrose with orthophosphoric acid (pH of 1.5) used to control nausea and vomiting of functional origin. The use of this undiluted syrup has provided satisfactory control of vomiting or regurgitation in infants and children. In addition, the phosphorated carbohydrate solution has produced measurable improvement in a significant proportion of cases of nausea and vomiting of early pregnancy. The mechanism of action remains obscure although the preparation has antispasmodic properties.

### DIGESTANTS

These substances are essentially replacement drugs used in the treatment of those clinical conditions where certain elements of the natural digestive process are lacking.

Studies have been conducted to determine the incidence of hypochlorhydria in various age groups. These investigations have revealed that with advancing years there is an increase in the number of persons who suffer from hypochlorhydria. Approximately 25 per cent of those studied, at age 60, failed to show free acid in the stomach on repeated fractional analysis. The decline in gastric acidity is not necessarily uniform with increasing age of a specific person. It has been variously estimated that the general population exhibiting a degree of hypoacidity varies from 10 to 15 per cent. The symptoms are few. There may be loss of appetite and a sense of fullness after eating. A few patients with this disorder may have symptoms resembling those of hyperacidity. A true achlorhydria is frequently associated with pernicious anemia and carcinoma of the stomach. For these reasons it is imperative that a gastric analysis be made to determine the amount of hydrochloric acid in the stomach.

**Azuresin, U.S.P. (Diagnex blue).** This is a complex of polyacrylic carboxylic acid resin and azure A dye and is used for the determination of gastric anacidity. The resin complex is an odorless, tasteless, amorphous, granular solid. It is nearly insoluble in water or dilute acids. After administration of the agent orally, the blue dye on the resin is displaced by the hydrogen ions of the hydrochloric acid of the stomach. A part of azure A dye, which is 3-amino-7-dimethylaminophenazathionium chloride, is absorbed and excreted in the urine within 2 hours after administration of the resin complex. A stimulant to gastric secretion is given 1 hour prior to the dose of the resin. Assay of the azure A content of urine specimens, collected at the end of a control 1-hour period and 2 hours after administration of the resin, indicates the presence or absence of free hydrochloric acid in the stomach. Thus, gastric achlorhydria can be detected without the discomfort of intubation for gastric analysis. The test does not furnish exact quantitative results, but it is convenient for screening patients with minor gastric symptoms that are not sufficiently severe to warrant intubation analyses.

**Diluted Hydrochloric Acid, N.F.,** is a 10 per cent solution of HCl. It is administered in doses of 4 ml. diluted with water or fruit juice in hypochlorhydria. The acid acts as a *stomachic* and releases pepsin from the pepsinogen of the parietal cells and provides an acid medium for pepsin action. The prolonged and continuous use of hydrochloric acid may deplete the bicarbonate content of the blood and give rise to an increased blood chloride concentration. In these patients an alkali-forming diet of citrus fruits and green vegetables will tend to combat the blood acid-base imbalance. The solution of diluted hydrochloric acid with 10 to 20 volumes of water is best administered by means of a glass drinking tube to avoid contact with the teeth.

**Glutamic Acid Hydrochloride, N.F. (Acidulin, Glutan, Glutansin)** is a combination of HCl with glutamic acid which in contact with water quickly yields hydrochloric acid. The compound is a white powder. In capsules, doses of 0.3 gm. administered before meals provide a supplemental amount of 0.6 ml of diluted hydrochloric acid. The drug in a 1-gm. dosage has given satisfactory clinical results.

**Betaine Hydrochloride (Normacid)** is a dosage form for hydrochloric acid therapy that provides in each tablet the equivalent of 1 ml. of dilute HCl. Each tablet contains 440 mg. of betaine hydrochloride, 32.4 mg. of pepsin, and 110 mg. of methylcellulose. The mixture is said to liberate hydrochloric acid slowly in the stomach, paralleling the normal release of acid in the process of digestion.

**Pepsin, N.F.,** is a powdered substance containing the enzyme obtained from the glandular layer of the fresh stomach of the hog. It is assayed by its capacity to digest from 3000 to 3500 times its weight of egg albumin. The dose is 0.5 gm.

Formerly, pepsin was prescribed to assist in the digestion of protein. There is no evidence to show that this enzyme is lacking in digestive dysfunction.

**Rennin, N.F.,** is the partially-purified milk-curdling enzyme obtained from the glandular layer of the stomach of the calf. It is assayed by its capacity to coagulate cow's milk.

**Pancreatin, N.F.,** is a substance containing enzymes, principally pancreatic amylase, trypsin, and pancreatic lipase, obtained from fresh pancreas of the hog or ox. It is a cream-colored, amorphous powder, having a faint, characteristic but not offensive odor. It is slowly but completely soluble in water. It converts 25 times its weight of starch into soluble carbohydrates and 25 times its weight of casein into proteoses. The dose is 0.5 gm.

Pancreatin is prescribed orally as an aid to duodenal digestion, *e.g.*, in sprue. Pancreatin acts only in an alkaline medium and is inactivated in the stomach.

### Gastrointestinal Adsorbents

These substances are neutral, chemically-inert powders having the capacity of adsorbing bacteria, bacterial toxins, or alkaloids on their large surface area. Many of the gastric antacids are also excellent adsorptive compounds. Adsorbents have a place in the treatment of food poisoning, in diarrhea caused by infection with a dysenteric organism, and in the treatment of acute poisoning resulting from the oral ingestion of a toxic substance.

**Kaolin, N.F.,** has been shown to "carry down" bacteria from a fluid medium and to adsorb the toxins of such organisms as *B. enteritidis*, *B. botulinus*, *B. typhosus*, and *B. paratyphosus*. It is administered in suspension with gum arabic or other demulcent suspending agents. A number of commercial forms of this preparation are available for therapeutic use. Among these are Kaomagma and Kaopectate. *Kaolin Mixture with Pectin, N.F.*, is an official dosage form. Neomycin may be incorporated in kaolin-pectin preparations as an anti-bacterial agent effective against intestinal microorganisms causing bacterial diarrheas.

**Activated Charcoal, N.F.,** is a fine, black, odorless, tasteless powder free from gritty matter. One gram is capable, by adsorption, of completely removing from solution 100 mg. of strychnine sulfate dissolved in 50 ml. of water by adsorption. Charcoal powders formerly occupied a favored place in the treatment of dyspepsia, flatulence, diarrhea, and dysentery.

Powdered charcoal is an effective antidote for poisons that have been taken by mouth. Of the many products available the National Clearinghouse for Poison Control Centers points out that Nuchar C, Darco G60, and Norit A are suitable. Bone charcoal is not satisfactory as an adsorbent antidote.

**Bentonite, U.S.P.,** is a native, colloidal, hydrated aluminum silicate. It is a very fine, odorless, buff-colored powder, free from grit, and insoluble in water. When added to water the dry powder swells to approximately 12 times its volume to form a gel. The compound has great adsorptive capacity. *Bentonite Magma, U.S.P.*, is a 5 per cent magma in distilled water. The magma is used in *Chalk Mixture, N.F.*, the average dose of which is 15 ml. Bentonite is an excellent suspending agent for insoluble powders and is widely used in many liquid pharmaceutic preparations and in ointments.

**Pectin, N.F.** "Pectic substances" is a group designation for those complex colloidal carbohydrate derivatives which occur in plants and contain a large proportion of anhydrogalacturonic acid units which are thought to exist in a chain-like combination. The carboxyl groups of polygalacturonic acids may be partially esterified by methyl groups. The general term pectin designates those water-soluble pectinic acids of varying methyl ester content and degree of neutralization which are capable of forming gels with sugar and acid. The official product is a purified carbohydrate mixture obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It is not the same as the commercial jellied food product.

Pectin for medicinal use as a protective and adsorbent is a coarse or fine, yellowish white, odorless powder with a mucilaginous taste. The substance is almost completely soluble in 20 parts of water forming a viscous, opalescent colloidal solution which is acid to litmus. Pectin is used as an emulsifying agent in pharmaceutic and cosmetic products.

When taken by mouth pectin preparations have been found to be useful in the symptomatic treatment of diarrhea. Its mechanism of action is unknown, but it is believed that the galacturonic acid polymers of pectin act as adsorbents for toxins, and in addition, these acids may provide an unfavorable environment for bacterial proliferation. The carbohydrate complex is decomposed in the intestinal tract. Commercial preparations of pectin are available in combination with kaolin.

**Lactobacillus acidophilus and Lactobacillus bulgaricus (Lactinex).** Cultures of these microorganisms prepared in tablet form have been found useful in reestablishing the bacterial flora in the gastrointestinal tract after antibiotic therapy. The diarrhea associated with the oral use of the broad-spectrum antibiotics has responded favorably following the administration of this type of therapy. The preparation is administered in doses of 2 to 4 tablets 3 to 4 times a day with a glass of milk.

### Contrast Medium for Gastric Roentgenography

**Barium Sulfate, U.S.P.** ($BaSO_4$), is a fine, white, odorless, tasteless, bulky powder, free from grittiness. It is insoluble in water. The compound is completely innocuous even when taken in the very large doses necessary to provide visualization of the gastrointestinal tract. The compound passes through the intestinal tract unchanged and renders the gut visible on the x-ray plate by its presence. For examination of the stomach 300 gm. of barium sulfate is suspended in approximately 400 ml. of water. This mixture is taken by mouth. For examination of the lower bowel approximately 500 gm. of barium sulfate is suspended in 500 ml. of mucilage of acacia and 1.5 L. of condensed milk. The patient is prepared by a previous enema, and the suspension, warmed to body temperature, is administered rectally by an enema tube.

The United States Pharmacopeia calls attention to the danger of writing a prescription for barium sulfate by abbreviation. When barium sulfate is prescribed, the title should always be written out in full to avoid confusion with the poisonous *barium sulfide* or *sulfite*.

### Cathartic Drugs

The physician must critically evaluate the requirements of the patient with respect to the selection and use of a cathartic drug. He must keep in mind that while constipation is perhaps one of the most frequent complaints encountered in medical practice, it is not a disease but a functional disorder of the colon. A large number of cathartic drugs are used, and there is a tendency of the public to resort habitually to purgatives. These drugs are usually taken without medical advice. As a result, chronic constipation associated with tolerance to these drugs is a common and perplexing medical problem. Good medical judgment dictates the use of cathartic drugs only in those cases where they are specifically indicated. In hospital routine an unnecessarily large number of cathartics are prescribed, and too frequently recourse is made to these drugs without careful consideration of the requirements of the individual patient.

The symptom of constipation may be relieved by a dose of a cathartic, but the basic cause will still remain. Further, it is important to remember that there are rather obvious contraindications to the use of cathartics. In addition, the discomfort to the patient, possible dehydration, loss of nutritive elements, and irritation to the gastrointestinal tract are not to be overlooked. The bowel-conscious subject fears that harm will come if he does not defecate each day. Consequently, he will take some purgative daily. The result may be similar to simple, prolonged diarrhea with symptoms of potassium depletion, intestinal hypotonus, alkalosis, and muscle weakness.

Some of the undesirable aspects of drug-induced constipation as these relate to the vascular system have been reviewed by Shaftel *et al.* (1960). A survey indicated a high frequency of vascular accidents associated with bowel function. The value of fecal softening agents in preventing undesirable straining forces during defecation has been demonstrated. The cerebrovascular, vertebral, cardiopulmonary, and peripheral vascular dynamics associated with the Valsalva maneuver as they relate to normal and abnormal intestinal function have been reviewed (Kramer *et al.*, 1960).

With the introduction of the fecal moistening agents and less toxic synthetic cathartic drugs, there seems to be little place for the irritant cathartics in medical practice. Fecal moistening agents, *e.g.*, dioctyl sodium sulfosuccinate, are effective in the treatment of constipation. These substances are not cathartics or laxatives. Their beneficial effect is exerted by softening the stool, which results in the restoration of normal function in terms of feces consistency and frequency of defecation. As benign, nonirritating substances in the intestine, these agents may be far more satisfactory for the control of spastic constipation than the irritant cathartic drugs.

The cathartic drugs may be classified according to their *site of action*, *chemical structure*, and *mechanism of action*. In this chapter these drugs are classified by their mechanism of action as follows:

1. Irritant cathartic drugs
2. Cathartics which increase the bulk of intestinal contents
3. Fecal softening agents
4. Intestinal lubricants.

**Regulation of movements of the intestinal tract.** The sympathetic nervous system, through the splanchnic nerves, is inhibitory to the course of the musculature of the gut. The parasympathetic nervous system, through the vagus and pelvic nerves, is motor to the course of the intestines. In addition, the psychic component of gastrointestinal function must not be overlooked. Sympathetic stimulation produces an arrest of movement and relaxation of the gut muscle. Parasympathetic stimulation brings about increased movement; strong stimulation will produce colic-like, vermiform contractions. For example, neostigmine, which stimulates structures innervated by cholinergic nerves, elicits such a response. This drug is used in stimulating intestinal activity and evacuation after abdominal operations when intestinal stasis persists. Very few cathartics are employed that act through the autonomic control of the intestine.

Most cathartic drugs act by producing irritation of the mucosa of the gut, and thus reflexly they stimulate increased activity and produce defecation. The character, degree, and extent of irritation differ with the various drugs. The cathartics that act by increasing the bulk of the intestinal contents distend the intestinal muscle and thus induce contraction. Posterior pituitary solution may serve as an emergency cathartic drug because of its effect in directly stimulating the intestinal musculature.

A number of terms are used to designate the cathartic drugs. The words *laxative*, *cathartic*, and *purgative* are employed interchangeably. The term *aperient* is frequently used to designate a mild saline cathartic, usually of the effervescing type. A *hydragogue cathartic* increases the movement of body water into the intestinal tract.

## IRRITANT CATHARTICS

**Anthracene compounds (emodin cathartics).** The botanical drugs *rhubarb*, *senna*, *aloe*, and *cascara* contain oxymethylanthraquinones, which are present in the drugs partly in a free condition but principally as glycosides. The glycosides are not active cathartics, but in the intestine they are decomposed gradually with the formation of active substances. *Emodin* (trioxymethylanthraquinone) and *chrysophanic acid* (dioxymethylanthraquinone) are the compounds found occurring most frequently in these vegetable drugs.

Emodin is the most important cathartic constituent. Its action is largely confined to the lowest portion of the intestine. Individuals taking the anthracene cathartics may excrete brown or yellowish colored urine, resulting from the excretion of these substances in the urine.

**Rhubarb, N.F.,** is the dried rhizome and roots of *Rheum officinale* and related species. It contains a high percentage of chrysophanic acid, emodin, and tannins. The plant is not the vegetable garden rhubarb that is an item of food.

In the form of *Rhubarb Fluidextract, N.F.*, this drug has been used as a mild cathartic in medical practice for many generations.

**Senna, N.F.,** consists of the dried leaflet of *Cassia acutifolia*, Alexandria senna, or *Cassia angustifolia*, Tinnevelly senna. The plant contains a number of constituents; the most important therapeutic principle is emodin. It is a relatively mild cathartic drug. The *N.F. Fluidextract of Senna* and *Senna Syrup* with doses of 2 ml. and 8 ml., respectively, are commonly prescribed dosage forms. There are many proprietary forms of this drug.

**Aloe, U.S.P.,** is the dried juice of the leaves of the plant *Aloe perryi* and related species. Aloe contains a mixture of active principles, chiefly glycosides and anthraquinone derivatives, that comprise *Aloin, N.F.* Aloin is a lemon yellow to dark yellow, microcrystalline powder. It is odorless and intensely bitter to the taste. In the intestine the glycosides are hydrolyzed, yielding active anthraquinone derivatives. Aloe and aloin may produce violent purging in some individuals. The dose of aloe for adults is 0.25 gm., and of aloin 15 mg.

**Cascara Sagrada, U.S.P.,** is the dried bark of the tree *Rhamnus purshiana* of southwest Canada and the northwest United States. The active principle is *emodin* which is present in the bark to the extent of 1.4 to 2 per cent. The extractive preparations are the dosage forms. The average dose of *Cascara Tablets, N.F.*, is 0.3 gm.; *Cascara Sagrada Fluidextract, N.F.*, 1 ml.; *Aromatic Cascara Sagrada Fluidextract*, U.S.P., 2 ml. Cascara acts mainly on the colon, producing evacuation without severe irritation.

**1,8-Dihydroxyanthraquinone (Dorbane).** This agent, chemically related to emodin, is a synthetic compound. It exerts a mild cathartic effect on the large bowel. The adult dose is 1 to 2 tablets containing 0.15 gm. of active ingredient in each tablet. The tablets are administered in the evening, and evacuation usually follows within 12 to 24 hours.

**Bisacodyl (Dulcolax).** Chemically this substance is bis(*p*-acetoxyphenyl)-2-pyridylmethane. It is a colorless, tasteless, practically water-insoluble compound. It is described as a "contact laxative" that produces its effect by direct action on the mucosa of the colon. The adult oral dose is two 5-mg. tablets.

**Phenolphthalein, N.F.,** is a white or faintly yellowish white, crystalline powder insoluble in water. It is odorless and stable in air. The small dose, its tasteless character, and mild cathartic action make it one of the most popular cathartic drugs. Phenolphthalein is probably dissolved in the small intestine in the presence of the bile and alkaline juices.

After the administration of an average adult dose of 60 mg., the drug usually produces catharsis within 4 to 8 hours.

*Toxicity of phenolphthalein.* In most individuals phenolphthalein is a nontoxic substance; however, idiosyncrasy is known to occur. In persons sensitive to phenolphthalein the reaction manifests itself as a polychromatic skin eruption with macular plaques of different size. The color of the lesions is usually deep pink, but they may be dark purple. The pigmentation may last for several months. These skin lesions are usually associated with an itching, burning sensation. In addition to skin lesions, idiosyncratic persons may experience diarrhea, cardiac and respiratory distress. These adverse reactions seem to be allergic in character since subsequent doses of the drug may precipitate a similar response. Although alarming to the subject, these reactions are not life-threatening, for fatalities have not been attributed to the use of phenolphthalein. This is remarkable in view of the wide, unrestricted use of the drug.

**Castor Oil, U.S.P.,** is the fixed oil obtained from the seeds of *Ricinus communis*. It is a pale yellowish oil with a faint, mild odor and a characteristic taste. Castor oil retains a popularity as a cathartic in spite of the development of the newer drugs that are taken in much smaller dosage.

The oil is a triglyceride of the unsaturated fatty acid, *ricinoleic acid*. In the alkaline juices of the intestine the oil is saponified, and sodium ricinoleate is formed which is irritating to the mucous membranes. The degree of irritation may be severe in some cases. The drug appears to act in the small intestine, and after the first period of 1 to 2 hours required for saponification, the action may move the intestinal contents very rapidly. Stools of a fluid character are produced within 6 to 10 hours. The degree of irritation in the small intestine may be sufficient to cause pelvic congestion. For this reason castor oil is contraindicated in menstruating and pregnant women.

**Ricin** is a toxic albumin present in the whole castor bean or seed. It is a white neutral substance soluble in water and exceedingly poisonous. A nitrogenous, water-soluble, related substance of a toxic character called *ricinine* has also been identified in the pressed cake remaining after the extraction of the fixed oil. An allergen has been recognized in castor seeds. The plant is commonly grown in flower gardens and has been the source of fatal poisoning. Children are the usual victims although death in an adult resulted from eating 3 seeds. Symptoms of ricin poisoning may not be manifest for several hours. They consist of nausea, vomiting, diarrhea, fall in blood pressure, convulsions, and collapse. The only treatment is symptomatic.

**Calomel, N.F.,** was at one time a very commonly used cathartic. In modern medical practice the drug has no rational use as a cathartic, and it should be relegated to a well-deserved oblivion. This drug is known as mild mercurous chloride.

## CATHARTICS THAT INCREASE THE BULK OF THE INTESTINAL CONTENTS

**Hydrophilic colloids. Agar, U.S.P.,** is the dried hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* and related red algae. Agar consists of hemicelluloses that are not digested to any significant degree in the intestinal tract. The substance absorbs water, forming a gel, and thus appreciably increases the bulk of the stool. Agar absorbs at least 5 times its weight of water at 25°C. with a corresponding increase in bulk. The mechanism of cathartic action involves the mechanical stimulus of distention. Since this is a normal stimulus, the action of substances of this type is perhaps least harmful of all the cathartic drugs. The mucilaginous, demulcent character of the gels and their lack of local irritation are additional advantages. When hydrolyzed, agar yields 3,6-anhydro-L-galactose and D-galactose as the chief constituent sugars.

The usual dose of agar is 4 gm. although very large doses can be taken repeatedly without harmful effects resulting from the agar *per se.* The advisability of continual ingestion of bulk-forming substances of this character is polemic.

There are a number of commercial preparations of emulsions of liquid petrolatum and agar that are used as cathartics. In these, such as *Petrogalar*, the liquid petrolatum is the principal cathartic ingredient.

**Plantago Seed, N.F. (Psyllium seed)** is the cleaned, dried, ripe seed of *Plantago psyllium* and certain related species. This seed contains a natural mucilage which imbibes water and swells in the intestine. Its mechanism of action is similar to that of agar. It is intended as an adjunct in the treatment of constipation rather than as a cathartic drug. The stool that results from the administration of this product is soft, water-retaining, and demulcent in character, so that it is safe to administer this substance in the presence of an inflamed intestinal mucosa.

**Psyllium Hydrophilic Mucilloid (Metamucil)** is a mixture containing about 50 per cent of the powdered mucilaginous portion of blonde psyllium seed, powdered anhydrous dextrose, and small amounts of inorganic salts. The average dosage is 4 to 7 gm. 1 to 3 times a day, each dose suspended in a glass of water followed by additional fluids.

**Methylcellulose, U.S.P. (Cellothyl, Hydrolose, Methocel, Syncelose).** Methylcellulose is the methyl ether of cellulose. The official product is the purified form of the commerical variety standardized on the basis of the methoxy content. It is a grayish white, fibrous powder that swells in water and produces a clear or slightly opalescent, viscous solution. The solution possesses demulcent properties.

Methylcellulose is used in chronic constipation. It converts the stools to a jelly-like consistency. When taken by mouth in doses of 1 to 4 gm., the powder absorbs water and swells, thus increasing the bulk of the intestinal contents. The bland, demulcent gel formed is not irritating to the intestinal mucosa. Methylcellulose has been very effective as a cathartic in patients with a reduced lumen of the sigmoid or ileum.

**Sodium Carboxymethylcellulose, U.S.P. (Thylose Sodium, Carmethose).** This product is the sodium salt of a polycarboxymethyl ether of cellulose. It is a light, odorless, hygroscopic powder easily dispersed in water to form a colloidal solution. Its action is similar to that of methylcellulose. The usual dose is 1.5 gm. 3 times daily with meals with 1 or 2 glasses of water. Tablets containing 0.5 gm. are available.

### Fecal Softening Agents

**Dioctyl Sodium Sulfosuccinate, U.S.P. (Doxinate, Molofac, Colace).** This substance is bis-2-ethylhexyl sodium sulfosuccinate. It is a surface-active agent known as Aerosol OT. As a wetting agent it encourages the admixture of fats and water. When taken orally, dioctyl sodium sulfosuccinate is essentially inert pharmacologically. It facilitates the mixture of water and fatty substances within the fecal mass apparently as a result of the lowered surface tension at the aqueous-lipoid interface. A homogeneous mixture is produced, and the feces assume a soft consistency. It is not known at present if this agent influences digestion or fat and vitamin absorption.

The use of dioctyl sodium sulfosuccinate in chronic constipation of the spastic type has resulted in effective fecal softening and the return of normal bowel function. The administration of dioctyl sodium sulfosuccinate has resulted in softer fecal masses in patients with impaction in the megacolon and anal fissure. In bedridden patients, especially children, the drug appears to be very useful.

The usual daily oral dose of dioctyl sodium sulfosuccinate for adults is 10 to 60 mg.; in infants and children 10 to 20 mg. is administered. Divided doses may give the best results. The stool-softening effect may not be evident for several days. Combinations of dioctyl sodium sulfosuccinate with cholic acid or bile salts are available. However, much of the advantage of using this agent in chronic constipation appears to be lost by combining its use with a cathartic drug.

**Poloxalkol (Polykol).** Poloxalkol is a surface-active agent with an oxyalkylene polymer structure similar to dioctyl sodium sulfosuccinate. The substance lowers the surface tension of intestinal fluids and tends to soften the stool and facilitate elimination. Because the substance is mild-acting, several days of therapy may elapse before its effect is evident. The drug seems most useful for infants and children. Its surface-active properties may modify the absorption of fats from the intestine. The dose of poloxalkol for adults and children over 6 years is 200 mg. 1 to 3 times daily; for infants and younger children, 100 to 200 mg. once or twice daily.

### Saline or Hydragogue Cathartics

These are soluble inorganic salts which are poorly absorbed from the gastrointestinal tract. Because they are absorbed only to a limited degree, these salts in solution retain and increase the water content of the feces. The action is osmotic in character. Saline substances are the cathartics of choice in the treatment of suspected poisoning and in individuals who have received antidotal treatment for orally-ingested poisons. They are quick-acting and less likely to injure further an inflamed mucous membrane. A liquid stool is produced within a few hours after the administration of a cathartic dose.

**Magnesium Sulfate, U.S.P.** ($MgSO_4 \cdot 7H_2O$, Epsom salt), is a colorless crystalline salt soluble in water 1:1. Its salty, unpleasant taste is objectionable. The dose is 15 gm. *Magnesium Citrate Solution, N.F.*, is a pleasantly-flavored effervescent solution. The adult dose is 200 ml. *Magnesia Magma, U.S.P.* (milk of magnesia) is a suspension of magnesium hydroxide containing approximately 8 per cent $Mg(OH)_2$. It is a cathartic drug that is acceptable by children. Administered diluted with a small amount of water or milk, the average laxative dose is 15 ml. It is also an antacid.

Magnesium ions are not absorbed to an appreciable extent from the intact intestinal mucosa. But because the level of blood-serum magnesium is critical, the administration of cathartic magnesium salts must be enjoined with caution in patients with intestinal irritation or obstruction. Using $Mg^{28}$ administered orally, it has been found that less than 10 per cent of the radioactivity is recovered in the urine of human subjects within 72 hours. Similar results have been obtained in animals. These findings suggest a low absorption of $Mg^{++}$ from the small intestine. Absorption of the $Mg^{++}$ ion does not appear to occur from the large intestine.

**Potassium Sodium Tartrate, N.F.** ($KNaC_4H_4O_6 \cdot 4H_2O$; Rochelle salt), is a white, crystalline powder soluble in water 1:1. The salt has an unpleasant taste, and since the average adult dose is 10 gm., an effervescent form has been popular. *Seidlitz Powders, N.F.*, consist of a mixture of 10 gm. of salts composed of 2.5 gm. of sodium bicarbonate and 7.5 gm. of potassium, sodium tartrate, and tartaric acid. As an aperient before the morning meal, the preparation is a satisfactory mild cathartic.

**Sodium Phosphate, N.F.** ($Na_2HPO_4 \cdot 7H_2O$), is prescribed as the *Effervescent Sodium Phosphate, N.F.*, a granular effervescent powder. An average adult dose of 10 gm. added to ½ glass of water forms a pleasant carbonated drink. It is generally used as an aperient.

**Sodium Sulfate, N.F.** ($Na_2SO_4 \cdot 10H_2O$, Glauber's salt), is a crystalline powder soluble in water. The sulfate ion is absorbed to a very limited degree in the intestinal tract, and a cathartic dose of sodium sulfate of 15 gm. exerts an osmotic retention of water in the gut with a resulting fluid catharsis.

### Intestinal Lubricants

Bland vegetable oils, insofar as they escape saponification, and mineral oil act as mechanical lubricants in the intestine. The laxative effect is associated with a softening of the fecal mass. These oils are not irritating to the intestinal mucosa and do not initiate an increase in peristaltic activity. They may, however, make normal intestinal movements more effective. There is some evidence that liquid petrolatum retains water in an emulsified form and thus tends to increase the fecal bulk. The lubricant oils may be desirable agents in those conditions in which some part of the lumen of the intestinal tract is reduced in caliber.

There are three serious objections to the use of liquid petrolatum as an intestinal lubricant. The substance interferes with the absorption of vitamins; it is absorbed especially in an emulsified form; and it may produce a lipid pneumonia. It seems important to stress these objections here even though they have been widely quoted in medical literature, because, in view of the popularity of mineral oil preparations, one wonders if they are recognized. This is especially true of routine hospital practice.

The repetitious use of liquid petrolatum may interfere with the absorption of carotene, the precursor of vitamin A. If the available vitamin content of the diet is critical, the continued use of mineral oil may prevent the absorption of an adequate vitamin supply. There is evidence also that the repetitious use of mineral oil may interfere with the absorption of other vitamins, as well as calcium and phosphate. It should be pointed out that these objections to the use of mineral oil as an intestinal lubricant are based upon long-continued use. There is no reason to believe that occasional administration of this substance will be deleterious, although some clinicians feel that it should never be used.

It has been shown that finely-subdivided liquid petrolatum oil in emulsified form may pass through the mucosa of the gut and be transported as a foreign substance throughout the body. The degree of absorption of the oil depends upon the fineness of the subdivision. This raises the question whether liquid petrolatum emulsion can be used with safety as an intestinal lubricant for long periods of time.

The third objection to the use of mineral oil is the lipid pneumonia which it may produce. When mineral oil is taken before retiring, the pharynx becomes coated by the soothing oil, and small droplets gain access to the trachea and eventually the posterior portion of the lower lobes of the lungs. The use of oil nasal drops may also produce this effect. A definite clinical entity is recognized as a reaction produced in the lungs which may appear on roentgenographic examination as a diffuse lesion or as a well-circumscribed granulomatous nodule. The latter form is sometimes confused with primary bronchogenic carcinoma (Forbes and Bradley, 1958).

In view of the serious indictments of liquid petrolatum as an intestinal lubricant, its use should be curtailed if not discontinued entirely in favor of superior cathartic agents.

**Liquid Petrolatum, N.F.** Mineral oil is a mixture of liquid hydrocarbons obtained from petroleum. The average adult dose is 15 ml.

**Liquid Petrolatum Emulsion, N.F.,** is an emulsion of liquid petrolatum with acacia or some other suitable suspending agent, pleasantly flavored. There are many proprietary forms in this preparation. Emulsions of liquid petrolatum with phenolphthalein, and with cascara sagrada, are also available.

**Olive Oil, U.S.P. (Sweet Oil),** will serve as a laxative oil in infants and adults. It may be taken at bed time in 1 adult dose of 30 ml. or in divided doses morning and evening. In infants 4 to 8 ml. is administered.

### Bile Salts

The bile of man and of certain animals contains the sodium salts of several conjugated oxycholanic acids of varying composition. The salts combine with glycine to form glycocholates and with taurine to form taurocholates. The glycocholates predominate in human and ox bile. The bile salts constitute the principal active portion of bile. They stimulate the secretory activity of the liver in promoting the flow of hepatic bile. It is claimed that they enhance the effectiveness of peristaltic activity and thus promote catharsis. Bile salts have been employed to promote the intestinal absorption of food fats and the fat-soluble vitamins. After absorption from the intestinal tract, the bile salts act as choleretics, *i.e.*, increase the output of bile by the liver.

The bile acids are classed as steroids and are hydroxy derivatives of cholanic acid.

**Cholic Acid** is 3,7,12-trihydroxycholanic acid and occurs in conjugation with glycine and taurine in bile. Cholic acid salts are the most important constituents of the medicinal preparations of the bile salts.

**Ox Bile Extract, N.F.,** contains an amount of the sodium salts of ox bile acids equivalent to not less than 45 per cent of cholic acid. It is a brownish yellow, greenish yellow, or brown powder. The material is extremely bitter and irritating to mucous membranes. Ox bile extract is soluble in water and in alcohol. The solution foams strongly when shaken. The average adult dose as a choleretic is 0.3 gm. administered preferably after meals in enteric-coated tablets as *Ox Bile Extract Tablets, N.F.*

**Dehydrocholic Acid, U.S.P. (Decholin).** Dehydrocholic acid, 3,7,12-trioxocholanic acid, increases the volume of bile secreted. It is a white, odorless powder eliciting a bitter taste. When administered by mouth as tablets in a dose of 0.25 to 0.5 gm. 2 to 3 times a day, the drug produces hydrocholeresis. This increased bile flow is believed to encourage drainage of the bile ducts by removal of mucus and to discourage the ascent of infection in these structures in cholecystitis. Its administration may aid the absorption of fat and assimilation of fat-soluble vitamins in cirrhosis of the liver and steatorrhea.

**Sodium Dehydrocholate Injection, N.F.,** is administered intravenously. It has the same

actions as dehydrocholic acid, but the effects are produced more promptly. It has been used to determine the arm to tongue circulation time in certain conditions where the velocity of blood flow may be reduced. The solution is injected into a cubital vein, and the time required for the perception of a bitter taste by the subject is recorded. The average normal time range has been found to be 9 to 16 seconds.

Dehydrocholic acid and sodium dehydrocholate are contraindicated in complete mechanical biliary obstruction. Their use in severe hepatitis is questionable because this condition may be aggravated by the hydrocholeretic effect. Sodium dehydrocholate is contraindicated in the presence of bronchial asthma because this salt produces effects resembling those of vagal stimulation. These substances must be employed with caution in patients with a history of allergy. A preliminary skin test is considered advisable in such patients.

### Agents for Cholecystography and Liver Function Tests

For diagnostic purposes certain radiopaque substances that are excreted in the bile are used for visualization of the gall bladder. They are organic iodine compounds that cast a shadow upon the x-ray film. These diagnostic agents are described in this section. In addition, liver function tests involving the use of chemical compounds or dyes are considered. A critique of the use of radiopaque diagnostic agents, their pharmacologic aspects, limitations, clinical appraisal, chemistry and history have been reviewed. (Poppel, 1959).

### Cholecystographic Agents Administered Orally

**Iopanoic Acid, U.S.P. (Telepaque)** is $\beta$-(3-amino-2,4,6-triiodophenyl)-$\alpha$-ethylpropionic acid. This substance is a cream-colored, tasteless powder, insoluble in water. It is administered orally as a radiopaque medium in cholecystography. The usual dose is 3 gm. administered orally 10 hours before the scheduled x-ray examination. Its use has seldom produced toxic reactions. It is contraindicated in acute nephritis and uremia.

In most patients the agent is promptly and adequately absorbed and eliminated in the bile or stored in the gall bladder in sufficient concentration to cast a dense shadow on the x-ray film. The drug is administered with several glasses of water during or after a light fat-free meal in the late afternoon. No food is eaten until the roentgenologic examination is completed the next morning. The substance should not be administered when gastrointestinal disorders may prevent the absorption of the compound. Iopanoic acid is available as 0.5-gm. tablets.

**Iodoalphionic Acid, N.F. (Priodax).** Iodoalphionic acid is $\beta$-(4-hydroxy-3,5-diiodophenyl)-$\alpha$-phenylpropionic acid. It occurs as white crystals or a faintly yellowish powder, having a faint, characteristic odor and taste. It is slightly discolored on prolonged exposure to light. The compound is insoluble in water and is administered orally in tablet form.

Iodoalphionic acid is used for roentgen-ray examination of the gall bladder. The compound is relatively nontoxic and is excreted by the kidneys. The average adult dose is 3 gm. *Iodoalphionic Acid Tablets, N.F.*, are available containing 0.5 gm. each.

Iodoalphionic acid is said to be less likely to cause nausea, vomiting, and diarrhea than iodophthalein sodium. It is contraindicated in acute nephritis, uremia, and severe gastrointestinal disorders. It may produce transient symptoms of nausea, headache, generalized itching, and a sensation of burning in the esophagus.

**Iophenoxic Acid, U.S.P. (Teridax),** is $\alpha$-ethyl-3-hydroxy-2,4,6-triiodohydrocinnamic acid. This is a water-insoluble organic iodine compound for oral administration. It is rapidly absorbed from the intestines, eliminated in the bile, and excreted chiefly in the urine. A single dose of 50 mg./kg. will produce satisfactory concentration in the gall bladder usually within 8 to 12 hours. The compound has a low systemic toxicity and few unpleasant side reactions. Nausea, vomiting, and diarrhea following the ingestion of iophenoxic acid may occur, but generally gastrointestinal disturbances have not been severe. A dose of 6 gm. should not be exceeded, and patients with advanced renal disease are not good risks for therapy with iodinated compounds of this character. *Iophenoxic Acid Tablets, U.S.P.*, are available containing 0.75 gm. each.

**Bunamiodyl Sodium (Orabilex).** This radiopaque organic iodine compound is sodium 3-(3-butyrylamino-2,4,6-triiodophenyl)-2-ethylacrylate. It is used as a roentgenographic contrast medium in cholecystography and cholangiography. After oral administration it is secreted in the bile and provides visualization of the gall bladder and biliary ducts. The same precautions must be observed with this drug as with other agents of this class.

The oral dose is 4.5 gm. taken as 750-mg. tablets at intervals of 2 to 5 minutes. The usual dietary routine for cholecystographic agents is followed.

### CHOLECYSTOGRAPHIC AGENTS ADMINISTERED INTRAVENOUSLY

Water-soluble organic iodine compounds are injected for visualization of the gall bladder and the biliary tract as x-ray contrast media. In addition, these agents are employed for excretory urography and their use in this manner is discussed in the chapter on the response of water balance to pharmacologic agents. The use of these substances for radiographic diagnosis by injection into body cavities, *e.g.*, bronchial tree, spinal canal, Fallopian tubes, and for venograms in the study of varicose veins, is not included in this text.

**Iodophthalein Sodium, N.F. (Tetraiodophthalein sodium).** Soluble iodophthalein is a pale blue-violet, odorless, crystalline powder, eliciting a saline and astringent taste. It is administered intravenously in 2-gm. doses for subsequent roentgenographic examination of the gall bladder. Because less toxic and more satisfactory oral agents are available, iodophthalein is seldom used.

**Sodium Iodipamide, N.F. (Cholografin).** The sodium salt is N,N′-adipyl-bis(3-amino-2,4,6-triiodobenzoate). This is a water-soluble organic iodine compound that may be administered intravenously for cholangiography and cholecystography. The use of this agent is restricted to those patients who are unable to ingest or absorb oral agents or in special cases when a rapid visualization of the gall bladder is essential for differential diagnosis in emergencies and prior to surgery. The drug is administered intravenously as a 20 per cent solution by slow injection into the antecubital vein. The usual dose for adults is 40 ml. of a 20 per cent solution. A preliminary sensitivity test must be carried out before the injection of sodium iodipamide. Conjunctival instillation of 2 drops of the solution should not produce an inflammatory reaction of the eye within 10 to 15 minutes. Intradermal injection of 0.1 ml. should not produce a wheal. A positive reaction to either of these tests indicates hypersensitivity, and the agent should not be injected.

Sodium iodipamide should not be administered to patients hypersensitive to iodides or to those with severe impairment of renal function. It is likewise contraindicated in patients with hyperthyroidism.

**Methylglucamine Iodipamide, U.S.P. (Cholografin methylglucamine),** has been found to be superior to the sodium salt. There are fewer side reactions with this salt, and a smaller volume is necessary intravenously to provide better visualization of the biliary tract.

**Sulfobromphthalein Sodium, U.S.P.,** was introduced as a test for liver function in 1925 by Rosenthal and White. The test depends on the fact that the compound is almost entirely excreted by the liver into the bile in normal individuals, and in liver dysfunction there is a delay in its removal from the blood. The amount of the dye remaining in the circulating blood determined at intervals following an intravenous dose is the basis of the test. The method measures the capacity of the reticuloendothelial system to remove the compound from the blood stream rather than the capacity of the liver cells to excrete it in the bile. From 85 to 95 per cent is removed from the blood in 30 minutes in a normal individual. The excretion in the bile requires from 1 to 3 hours. Obstruction of the common duct does not prevent the removal of the dye from the blood stream at a normal rate.

The administration of 5 mg./kg. intravenously is followed in 1 hour by the estimation of the dye in the circulating blood. The retention of 6 per cent or less of the dye is considered normal. Impairment of liver function will show a greater retention of the dye.

Other methods of determining liver function have been devised, such as the galactose test, bilirubin clearance test, the tyrosine test, and the phosphatase test. A description of these tests is beyond the scope of this text. However, it should be noted that accurate liver function tests are desirable to assess the hepatic toxicity of drugs. Not any of these methods that are currently available are entirely satisfactory to evaluate liver dysfunction.

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# PART IV

## THE RESPONSE OF THE CENTRAL NERVOUS SYSTEM TO DRUGS

## 20

# *Physiologic and Pharmacologic Considerations of the Central Nervous System*

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The central nervous system is the most highly organized of all the systems of the body. It may be thought of as being superimposed upon all other organ systems for the purpose of coordinating their diverse functions toward a smoother functioning of the organism as a whole. It subserves the phenomenon of *consciousness* which is one of the most intriguing, yet baffling, manifestations of living matter. Generally speaking, however, the central nervous system functions as an aid in the adjustment of the organism to its environment. Such adjustment, to both internal and external environments, is essential for survival and is carried out by a series of highly specialized tissues and organs. In sequence these are: first, the *receptors*—those peripheral neural structures which are stimulated by environmental changes; second, the *afferent fibers*, which transmit the receptor impulses to the spinal cord and brain where correlation and integration take place. *Efferent fibers* then transmit the outgoing impulses to the appropriate effector organs, which respond to establish equilibrium and to achieve satisfaction for the individual.

**Subdivisions of the central nervous system.** For review purposes the following functional divisions of the central nervous system will be helpful. The *cerebrum* or *telencephalon* is the highest of the nerve centers and consists of two cerebral hemispheres. Superficially, these contain the cerebral cortex, which projects fibers to the deeper portions of the brain and spinal cord as *pyramidal* and *extra-pyramidal tracts.* It has been thought for some time that the cerebral cortex subserved the functions of conditioned reflexes, inhibition of certain reflexes, perception, sensation, association, memory, and that state of awareness known as consciousness. Recent evidence indicates that it is a correlation center between the incoming sensory impulses and the outgoing motor responses, producing specific and refined responses to various stimuli and environments. The cerebral cortex has been divided into overlapping motor, sensory, sensory-psychic, and association areas. Transverse fibers connect the 2 hemispheres with each other, while other tracts link the cortex with a group of basal ganglia.

The *basal ganglia* are masses of gray matter within the white matter of the telencephalon. These include the *corpus striatum* (*putamen, globus pallidus*, and *caudate nucleus*) to which are sometimes added the *amygdala, subthalamus* and *claustrum.* The corpus striatum is connected functionally with the *thalamus, subthalamus*, the *red nuclei* and the *substantia nigra* of the midbrain. It functions in the regulation of muscle tone and in the integration of *automatic* somatic motor functions. This system is thus partly responsible for *automatic* coordinative control.

The *thalamus* is a gray sensory nuclear mass which is functionally subdivided into *anterior, medial*, and *lateral nuclei.* The thalamus receives sensory impulses from the body and relays them to the sensory areas of the cerebral cortex. Impulses derived from stimuli such as pain, pressure, and extremes of temperature, upon arriving in the thalamus, give rise to a "crude awareness" which is an indiscriminating type of consciousness.

The *hypothalamus* lies ventral to the thalamus. It contains higher centers for the control of the autonomic nervous system and its varied homeostatic functions. It, therefore, contains nuclei which regulate body temperature, water balance, and the metabolism of carbohydrates and fat. In addition, the hypothalamus also houses centers for regulating sleep, thirst, and appetite. Neurosecretory centers are also located in the hypothalamus. They synthesize endocrine substances formerly thought to be produced in the hypophysis. It is also thought that the hypothalamus regulates the secretory activity of the anterior lobe of the hypophysis through a humoral mechanism.

**Midbrain, pons, and medulla oblongata.** These structures make up the *brainstem* and contain the cranial nerve nuclei and the ascending and descending nerve pathways to and from the cerebrum and cerebellum. Some anatomists include the hypothalamus with the structures composing the brainstem. Many important physiologic centers lie in this area, especially in the medulla oblongata, which has therefore been designated "the vital node." Among these are the nuclei which control respiration, cardio-inhibition, cardio-acceleration, vasomotor-tone, defecation, deglutition, vomiting, and coughing. The respiratory area extends to the pons, and a micturition center lies between the lower midbrain and the pons.

**Red nuclei.** These nuclei are located in the midbrain and receive fibers from the cerebellum, globus pallidus, and the cerebral cortex (middle frontal gyrus and the marginal area of the central fissure). They give rise to the *rubrospinal tracts* and the *reticulospinal tracts* which help regulate muscle tone and coordination.

**The cerebellum** serves to synergize volitional motor movements, control posture, and coordinate sensory stimuli which are concerned with the maintenance of equilibrium.

**Reticular formation.** The reticular formation is composed of small masses of gray matter separated by fine bundles of nerve fibers connected with the principal sensory and motor pathways. It extends from the upper portion of the spinal cord forward through the medulla, the pons, and midbrain to the diencephalon. The reticular formation has elaborate afferent connections in the central nervous system and sends efferent impulses to the associational areas of the cortex and lower levels of the central nervous system. It serves as a kind of reinforcing or background function of the central nervous system, augmenting reflex and voluntary movements to a state of optimal facility. It also serves to inhibit exaggerated movements. The reticular formation is concerned with the states of wakefulness and sleep and the perception of pain. It is drug vulnerable, for example, it is stimulated by amphetamine and depressed by barbiturates. The finer pharmacologic profile of any drug acting upon the central nervous system should include the response of the reticular formation.

**The spinal cord** serves as a reflex center. It is also traversed in its more peripheral part by a series of fiber pathways which conduct impulses either to or from the brain. These tracts are therefore divided into ascending and descending spinal pathways.

The principal ascending conduction pathways are:

1. Fasciculi gracilis and cuneatus. These are found in the posterior columns of the spinal cord and transmit muscle (kinesthetic impulses) and refined tactile impulses destined to reach consciousness.
2. Dorsal spinocerebellar tract, transmitting unconscious muscle sense.
3. Ventral spinocerebellar tract, transmitting unconscious muscle sense.
4. Lateral spinothalamic tract, for pain and temperature sense.
5. Ventral spinothalamic tract, for crude tactile sensibility.

The principal descending conduction pathways are:

1. Lateral cortico-spinal tract and ventral cortico-spinal tract, for voluntary control of striated muscle.
2. Rubrospinal tract and the related reticulospinal tract, for involuntary control of striated muscle.

### General Pharmacologic Considerations of the Central Nervous System

Because of its complex structure and delicate ramifications, the central nervous system is extremely sensitive to the action of drugs. Such drugs which do affect this system either stimulate or depress its activity. The result of stimulation may extend from slightly increased alertness to mania and convulsions. Depression may likewise vary from mild sedation to complete obliteration of consciousness and absence of all motor activity such as occurs in general anesthesia. The various parts of the central nervous system respond to the presence of drugs in a specific manner.

**The response of the brain to drugs.** Drugs in their usually prescribed dosage may affect only one particular portion of the central nervous system. When this dose is exceeded, however, the effect of the drug spreads so that the entire central nervous system may become influenced by its action. For example, small amounts of *caffeine* cause a mild stimulation of the perceptive and associative (psychic) areas. In larger doses it also stimulates the respiratory centers. The effect of such spreading is readily demonstrated in cats or dogs in which large doses of caffeine serve as a convulsant poison.

*Alcohol* depresses the reticular formation and the centers of inhibition in the cerebral cortex and thus permits a freer discharge of emotional activity. Larger doses of alcohol affect the medulla oblongata, thereby depressing the respiratory centers.

*Anesthetics* such as ether, chloroform, and nitrous oxide depress the sensory and motor areas of the cerebral cortex and the reflex centers in the spinal cord. If larger amounts are administered and their concentration in the blood is further increased, they also depress the respiratory centers.

*Phenobarbital* depresses the sensory and motor areas of the cerebral cortex. *Diphenylhydantoin sodium* depresses only the motor areas of the cortex. Both of these drugs are used in the treatment of epilepsy. Diphenylhydantoin sodium is especially useful because it specifically depresses the hyperexcitable motor cortex without dulling the psychic (perceptive and associative) functions of the patient.

*Pentylenetetrazol* produces marked stimulation of the motor areas of the brain. In addition, it stimulates the respiratory centers. In small doses the brain wave pattern of the motor area response may resemble that of *petit mal* epilepsy. With larger doses, such as those that were formally given intravenously in the "shock treatment" of psychiatric patients, the convulsive response is indistinguishable from the convulsive seizures of *grand mal* epilepsy.

The drugs which are used to reduce fever act in the region of the hypothalamus. It is believed that the salicylates and other antipyretics lower body temperature, in part at least, by their action on this region of the brain.

*Morphine* increases the threshold to pain. It acts mainly on the sensory areas in the cerebral cortex so that muscular tone is hardly altered. While it depresses the respiratory and cough centers of the medulla oblongata, it stimulates the closely neighboring vomiting and vagus centers. There is no adequate explanation for this high degree of selectivity.

Analgesic drugs which relieve integumental pain without depressing mental activity probably spare the cerebral cortex. Such drugs exert their action on the thalamus by preventing the pain impulses arriving through the lateral spinothalamic tracts from being relayed to the sensory areas of the cerebral cortex.

*Mescaline and lysergic acid diethylamide (LSD)* in very small quantities so affect the cerebral function that thinking disturbances which resemble schizophrenia are produced. The syndrome is antagonized by the administration of such *anti-hallucinogenic* drugs as chlorpromazine and reserpine. This comparatively new field of *psychopharmacology* presents one of the most striking advances in the field of drug therapy.

**Behavioral effects of drugs.** Since the advent of the widespread use of the psycholeptic or tranquilizing drugs in medical practice, pharmacologists are employing more of the technics of the psychologist to detect the effect of various drugs on behavior and mood. The screening process is usually carried out on laboratory animals, and the results, if possible, are extrapolated to man. For example, such characteristics as sociability, contentment, excitement, and hostility elicited by various drugs can be evaluated by carefully controlled observations of their effects in domestic cats. The suppression of the fear, hostility, and jungle-bred characteristics of the *Macaca rhesus* monkey is a typical behavioral response to most of the psycholeptic drugs.

Another procedure is a study of the modification by drugs on simple schedules of performance of pigeons or other animals. If the food is beyond the reach of the pigeon, it can be obtained by pecking a key. This can be further complicated by flashing various-colored lights on the operational key. Only one color light will make the food available when it is shown on the key and pecked by the pigeon. Once a norm of the animal's performance is established, the modification, either detrimental or improved, by the action of a drug can be studied.

Conditioned performance studies are often conducted on rats. Hungry animals may be rewarded in their cages by food available to them only by passing over a grid which shocks them. By pressure on a bar they may cut off the current or avoid shock by a circuitous route around the grid. Once a norm of the performance is established, the animal then is used to test the effects of drugs on its capacity to avoid the shock and achieve the reward. These and many other behavioral tests are acquainting the pharmacologist with a more definitive pharmacologic profile of the behavioral effect of drugs.

**The response of the spinal cord to drugs.** When drugs possessing a local anesthetic effect are injected into the subarachnoid space, the spinal nerves are blocked at their points of exit from the intervertebral foramina. Both motor and sensory fibers are affected. The production of spinal anesthesia depends upon this action.

*Strychnine* acts with specificity on the spinal cord, producing hyperreflexia. The nerve cell bodies of the dorsal horn sensory neurons, of the ventral horn motor neurons, and of the intervening connector neurons are all affected simultaneously. In small doses the action remains restricted to the spinal cord. Larger doses, however, produce an ascending effect which reaches the medulla oblongata.

*Curare*, like strychnine, is also a spinal cord stimulant. However, its depressant peripheral action at the neuromuscular junction of skeletal muscle nullifies its stimulating effect upon the spinal cord.

*Morphine* and its mono- and dimethylated derivatives, *codeine* and *thebaine*, respectively, increase the excitability of the spinal cord. The depressing cerebral effect of morphine masks its stimulating action on the cord, which is readily detectable in the decerebrate frog. Furthermore, morphine effectively blocks pain impulses from reaching the higher centers through the lateral spinothalamic tracts. Light touch impulses, however, which reach the cortex over the posterior columns and the ventral spinothalamic tracts remain relatively unimpaired by morphine.

### Tests for Central Nervous System Response to Drugs

Many tests have been devised to determine the qualitative and quantitative response of the central nervous system to drugs. For those which affect the perceptive and associative (psychic) acuity of man the established methods of psychology for measuring mental alertness are employed. When such drugs are not yet available to man, and the tests must be confined to laboratory animals, greater difficulties are encountered in the execution and interpretation of the tests.

**The loss of consciousness.** General anesthetics produce a progressive diminution of consciousness. As the anesthetic reaches the central nervous system, a preliminary stage of excitation occurs. The organism through its nervous system is striving to maintain contact with the environment. With continued administration of the anesthetic this excitatory phase rapidly gives way to depression. Mental faculties are quickly lost; speech becomes incoherent. If from the beginning the patient had been instructed to count, as the anesthesia deepens enunciation grows hazy, the counting becomes irregular, and is finally obscured by the dulling of consciousness. Cutaneous sensation disappears, reflexes become depressed, and motor activity is obliterated. The corneal and wink reflexes are finally abolished, indicating the loss of consciousness as the stage of surgical anesthesia is reached.

**Mental acuity tests.** Narcotic drugs interfere with mental functions, such as memory and the association of ideas, which are so essential for the performance of skilled activity. The subject under the influence of a narcotic drug may experience difficulty in recalling events which are a definite part of his memory pattern. Narcotic drugs are frequently tested by studying their effects on work which requires conditioned reflexes and memory for its successful performance. A person is given a task which is based upon the association of ideas, such as typing a manuscript or shooting at a target. He is required to repeat the assignment until further practice fails to improve his precision or increase his speed. The narcotic drug, for example, alcohol, is then administered. The subject, while under the influence of the drug, is then asked to perform the same task. Since alcohol depresses the higher sensory and associative areas of the cerebral cortex, its effect is evidenced by a diminution in the speed and an increase in the number of errors made in the test performance.

On the other hand, drugs such as caffeine, which stimulate the sensory cortex and reticular formation increase alertness. They tend to improve the accuracy and diminish the time of pretest performance.

It is well known that tests of this kind can be performed on laboratory animals preliminary to the use of the drug in man. For instance, rats may be trained to run for food in a circular maze containing many blind alleys. Upon repeated performance the number of blind alleys into which the animal enters is reduced to a minimum. The period of time consumed in reaching the food can be reduced no further by practice. Then the drug is given, and the observations are repeated.

The evaluation of tests such as these, whether they are applied to man or to lower animals, is extremely difficult. There are so many factors of individual variation that it is always necessary to conduct a large series of determinations in order to ascertain that the observed stimulation or depression of mental functioning has actually resulted from the drug being tested. In man, for example, the mere will to compensate for a mental impairment is in itself an important consideration. An alcoholic, even while under the influence of the drug, may be conditioned to perform a certain task, such as playing the piano, very well. While drunk he may exercise his will to concentrate on the performance of the task and under the duress of his strong volition may continue to compensate through concentration for a long period during his performance. With sufficient dosage, however, his will finally succumbs to the influence of the narcotic, and the performance will suddenly fail.

**Motor response tests.** The tests for motor response are frequently those which are used in physical diagnosis to evaluate reflex motor activity, for example, the patellar reflex. One must then determine whether the drug spares, delays, or accentuates the reflex. Narcotics in general when administered in sufficient doses diminish the extent of the motor response and increase the reaction time. Strychnine augments the reflex response, which then becomes brisk and accentuated.

Certain drugs such as curare and succinylcholine produce marked relaxation of skeletal muscle. Their effects are brought about by their action at the neuromuscular junction. They are used to produce relaxation in anesthesia. Their potency is determined by observing the amount required to produce that degree of flaccidity of the neck muscles of a rabbit which just prevents the animal from raising its head (head drop method). Consciousness is not lost.

The efficiency of motor response may also be determined by tests such as target shooting, driving an automobile and mountain climbing, where judgment and motor response must be highly correlated for well-coordinated performance.

**Pain intensity tests.** Perhaps the most widely used drugs are those which relieve pain. These are classed as the *analgesics*. The proper therapeutic evaluation of such drugs depends upon the ability of the pharmacologist to produce a quantitative pain stimulus in laboratory animals and man. Further, one must be able to measure the drug-induced diminution of the pain stimulus as it arrives in the cerebral cortex and other higher centers.

Much progress has been made in this field of investigation, especially since the Wolff-Hardy-Goodell apparatus has become available. This apparatus permits a focused light of definite intensity to shine over a circumscribed area on the blackened forehead of the subject. The time for the threshold response to pain is determined. When the subject (animal or man) is under the influence of an analgesic drug, this time period is generally increased. This procedure, of which there are many modifications, is also applicable to many types of animals. Although it has its drawbacks, this simple test has greatly facilitated a more precise evaluation of the central nervous system response to pain stimuli under the influence of drugs.

Drugs such as alcohol and scopolamine, which dull the memory and diminish the power of attention, also obtund pain in human subjects. Although these substances are primarily amnesia-inducers, their over-all pain-relieving effect compares favorably with that produced by the more specific analgesics.

# 21

# *The Response of the Central Nervous System to Depressants. Alcohol and the Alcohols*

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One of the primary concerns of the pharmacologist is with drugs ingested by man and other animals. The study of alcohol in the human body has consequently been an important problem for the pharmacologist, and his findings have elucidated the general sociological study of alcoholism. In the very beginning of this discussion let us propose the basic questions, important to the physician and the approximately 70,000,000 users of alcoholic beverages in this country: what is alcohol, and what becomes of alcohol when ingested?

### WHAT IS ALCOHOL?

The generic term *alcohol* in chemistry is used to designate an important class of compounds which are *hydroxy derivatives of aliphatic hydrocarbons.* Alcohol, without further description, refers to the second member of this class, namely, *ethyl alcohol*, $C_2H_5OH$. The synonyms *ethanol*, *grain alcohol*, and *proof spirit* are also employed. Unless modified by additional description, alcohol refers to 94.9 per cent by volume of ethyl alcohol. The remaining approximately 5 per cent consists chiefly of water with which alcohol forms a constant boiling mixture at about 78°C.

The word "alcohol" is derived from the Arabic *alkohl*, originally designating a collyrium, a very fine powder of antimony for staining the eyelids. When a happy drinker designates his liquor as an "eye wash," little does he realize how exactly his expression falls in with the etymology of the word. In 1624 Ben Jonson in "The Fortunate Isles" stated, "And truly alcohol has colored many an eye."

### THE FATE OF ALCOHOL IN THE BODY

When alcoholic beverages, especially distilled drinks such as whisky and brandy, are ingested, the alcohol is rapidly absorbed from the stomach, duodenum, and small intestine and is carried to all parts of the body by the blood. Scarcely any alcohol reaches the large intestine. The absorption of alcohol from the intestinal tract is extraordinarily rapid, particularly when the stomach is devoid of food. The concentration will reach its peak in the blood within 10 to 30 minutes.

Alcohol is oxidized rapidly in the tissues of the body. The oxidation is carried through to carbon dioxide and water according to the following equation:

$$C_2H_5OH + 3O_2 \rightarrow 2CO_2 + 3H_2O$$

The completeness of this metabolic process is dependent upon various conditions. The speed of alcoholic intake and the metabolic rate of the individual are factors. As a first approximation, a 70-kg. person can oxidize about 12 ml. of ethanol in an hour without symptoms. Although these data were obtained by studies on dogs by various investigators, they seem to hold within reasonable limits for the speed of metabolism in man. Newman (1949) studied this problem extensively and showed that a 70-kg. man can metabolize about 26½ ounces (751 gm.) of 100 proof whisky in 24 hours. Any appreciable increase above this amount would raise the alcoholic content of the blood and brain to a point where coma would supervene. Habituation, according to Newman, did not accelerate the speed of metabolism. Large and heavy individuals owe their increased capacity to metabolize alcohol to their increased bulk alone. Newman's data with regard to whisky, given above, are the approximate equivalents of 19 ml. of ethanol an hour. Later (1952) the same investigator administered 20 per cent alcohol solution to 4 individuals and studied the rate of metabolism. He found the maximal metabolism in this series to be 760 ml. of 100 proof liquor, and the minimal, 383 ml. Previous excessive drinking had no significant effect. These values average approximately 12 ml. of absolute alcohol per hour. It appears that there are tremendous variations in the capacities of different individuals to oxidize ethyl alcohol. Nevertheless the average is about 12 ml. per hour.

Bartlett and Barnet (1949) fed alcohol with a radioactive carbon atom, $C^{14}$, to rats and studied the fate of the compound in the body by means of tracer technics. It was observed that 75 per cent of the ethanol was oxidized within 5 hours, and 90 per cent had disappeared in 10 hours. Habituated rats, similar to tolerant human beings, did not enjoy an accelerated rate of metabolism. The evidence of the nearly complete utilization of alcohol in the animal organism appears to be confirmed by various investigators in different species.

When quantities of alcohol which exceed 12 ml. per hour are ingested, the alcoholic concentrations of the blood and other tissues are increased. Under these conditions from 1 to 5 per cent of the alcohol ingested is excreted unchanged. The larger portion of the unmetabolized compound passes through the kidneys in the urine, and the remainder is excreted by the lungs in the exhaled air.

Marshall and Fritz (1953) showed that there were no differences in the arterial and venous blood alcohol levels of dogs to which alcohol had been administered. The blood concentration is somewhat higher than that of the other tissues, but alcohol is distributed rather uniformly in the body. In a study of 53 dogs, Harger *et al.* (1937) showed the following distribution ratios for alcohol: brain, 1.00; blood, 1.17; liver, 0.91; and musculature, 0.90. All of the body tissues except the reticular formation and the cerebral cortex appear to be unaffected by a single dose of alcohol.

From the available evidence it appears that the primary site of the metabolism of alcohol is the liver. Here alcohol dehydrogenase removes 2 atoms of hydrogen, forming acetaldehyde. Acetaldehyde in its hydrated form is acted upon by aldehyde oxidase, which catalyzes its oxidation to acetic acid. Acetic acid is then oxidized to carbon dioxide and water.

**Does normal blood contain alcohol?** It is well established that the degradation of glucose in the body to carbon dioxide and water passes through the *lactic acid* → *ethyl alcohol* → *acetic aldehyde* stages. It would then follow that the blood and other tissues of total abstainers should contain alcohol. Indeed the existence of the degradation product of glucose, alcohol, might be exceedingly short-lived. Nevertheless, with refined methods its presence should be capable of detection.

This matter was put to rigid test by Gettler *et al.* (1932). These investigators used very ingenious micromethods for the analysis of alcohol in human and animal tissues. Alcohol had not been previously ingested. They isolated pure anhydrous ethanol in microquantities.

In more than 600 analyses of the bloods, brains, and livers from humans, pigs, and dogs, they found no sample negative to the qualitative test for alcohol. The average amounts of ethyl alcohol normally present in body tissues was:

Human brain, 0.4 mg. per cent
Human liver, 2.6 mg. per cent
Human blood, 4.0 mg. per cent
Dog brain, 3.0 mg. per cent
Dog blood, 1.3 mg. per cent
Pig brain, 0.07 mg. per cent

From their studies, Gettler and his associates concluded that "pure anhydrous ethyl alcohol was isolated and identified from the brain, blood, and liver of non-alcoholic humans, dogs, and pigs."

McManus *et al.* (1960) confirmed the earlier findings of Gettler on the presence of endogenous ethanol in the tissues of animals and man. They found from 23 to 145 $\mu$M/100 gm. of tissue: the human liver contained the highest amount of the tissues studied. Radioactivity from pyruvate-2-$C^{14}$ appeared in ethanol after incubation with liver slices, suggesting endogenous synthesis of ethanol.

Lester (1961) reviewed the status of ethanol as a normal endogenous metabolite. He concluded that the evidence was unequivocal that ethanol is present in human tissues, resulting from endogenous formation and not from bacterial fermentation in the intestinal tract. It appears that ethanol concentrations vary greatly from individual to individual. Also it was observed that the ethanol level in tissues is increased by hypoxia. The normal serum level for man appears to lie between 2 and 3 mg. per cent. Lester proposes the possibility of the causal relationship between endogenous tissue alcohol levels and the craving for alcohol. He suggests that an individual who has a low rate of ethanol synthesis and a deficiency in his capacity to utilize acetate might crave the ingestion of alcohol. The approach is interesting and might conceivably lead to either treatment or prophylactic procedures in alcoholism.

**Alcohol blood levels.** When the stomach is empty and alcohol is ingested, it can be detected in the blood within 5 minutes after it is taken. The maximal concentration in the blood is reached within 1 hour, and the curve of concentration descends slowly as the compound is metabolized. The blood concentrations experienced are dependent upon several factors. First, they are a function of the dose. Second, they vary directly with the concentration of the alcohol in the fluid ingested. Third, they are greater when the beverage is devoid of starches that delay absorption. Fourth, as indicated previously, the absence of food in the stomach favors rapid absorption.

The effect of the ingestion of whisky on the blood concentration of alcohol is shown in figure 21-1.

**The food value of alcohol.** Within limits, alcohol is a food. It is readily metabolized, it requires no digestive process prior to metabolism, and it is rapidly absorbed from the upper portion of the gastrointestinal tract. Alcohol does not serve as a reserve food, as does glucose. It cannot be stored in the liver as glycogen for subsequent utilization. In the metabolism of alcohol in the animal organism it serves, within limits, as a substitute nutrient for carbohydrate, protein, or fat. An increase in metabolism comparable to the alcohol oxidized therefore results. From the equation expressing the oxidation of alcohol the respiratory quotient is calculated as follows:

$$C_2H_5OH + 3O_2 \rightarrow 2CO_2 + 3H_2O$$
$$2CO_2/3O_2 = 2/3 \text{ or } 0.67$$

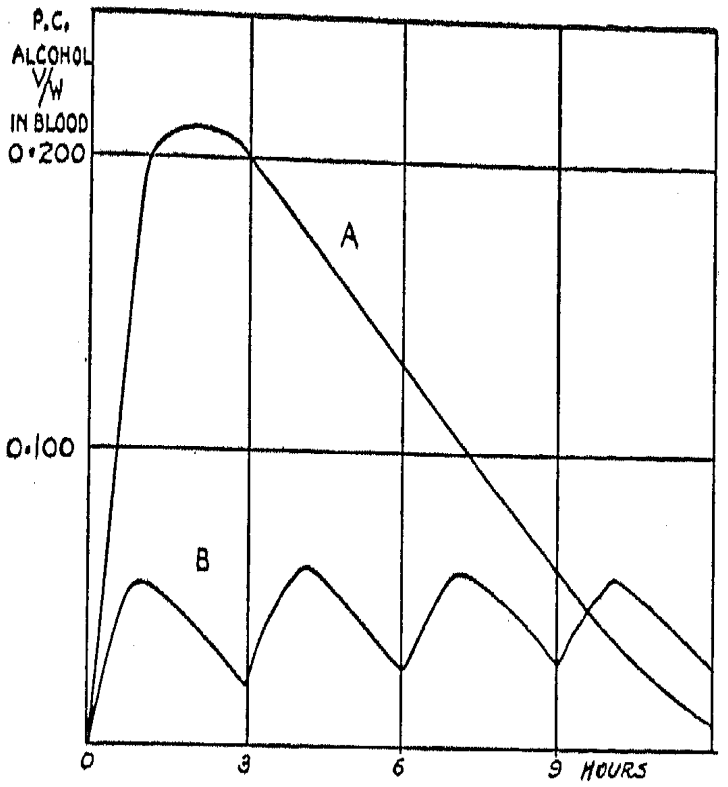


FIG. 21-1. Relation between intake and content in blood of alcohol in man. *A*, effect of 100 ml. of alcohol (= 8 fl. oz. whisky) taken in 1 dose; *B*, effect of 30 ml. of alcohol (= 2½ fl. oz. whisky) taken every 3 hours. (From A. J. Clark, *Applied Pharmacology*, J. & A. Churchill, Ltd., 1942.)

Therefore, if alcohol is oxidized in appreciable quantities in the body, the respiratory quotient is correspondingly lowered. A marked lowering of the R.Q. occurs in the human being for 1½ hours after taking 30 ml. of alcohol and for 3 hours after taking 50 ml. of alcohol (Carpenter and Lee, 1938). The rise in the R.Q. following the ingestion of glucose or levulose can be effectively nullified by the concomitant ingestion of alcohol, indicating the simultaneous metabolism of the two classes of foods.

Carbohydrates exhibit definite protein-sparing activity in the diet. Alcohol, like carbohydrate, is capable of sparing protein. Atwater and Benedict (1902) showed that individuals ingesting large quantities of alcohol experience the replacing of both fat and carbohydrate by alcohol metabolism. In fact, in their experiments alcohol supplied 25 per cent of the total energy output of the diet. In chronic alcoholics the classic picture of the protein effect of alcohol may be reversed (Tremolieres, 1962). Alcoholic cirrhotics are frequently protein-depleted. This is a manifestation of the toxic effect of alcohol rather than of its benign action at a low dosage level.

The caloric value of alcohol in the diet lies between that of carbohydrate (4 calories per gm.) and that of fat (9 calories per gm.). One gram of alcohol supplies 7 calories; therefore a pint of whisky will supply approximately 1400 calories.

The caloric value of alcohol in the human diet is a matter of common observation. In many individuals alcohol appears to spare carbohydrate. This allows carbohydrate to be stored as fat. Many individuals add many calories to their diets in the form of alcohol without their knowing its food value.

**Alcohol and the metabolic rate.** The rate of alcohol oxidation in the body has been the subject of many investigations. Wide species variations have been observed. The white rat oxidizes alcohol twice as rapidly as does man (McNaught and Pierce, 1939). A 13.5-kg. dog required 20 hours to oxidize 50 ml. of alcohol. In man, 25 to 30 gm. disappeared in 4 hours.

Perman (1962) infused rabbits anesthetized with urethane with alcohol, 200 to 400 mg./kg. There was an immediate increase of 10 to 15 per cent in oxygen consumption and a delayed increase in blood glucose level that averaged 70 mg. per cent. The hyperglycemia was believed to be due to the increased secretion of epinephrine evoked by alcohol or one of its metabolites. Although there has been much study of the effect of muscular activity upon the rate of oxidation of alcohol in man and animals, the question is still in dispute. For example, Hebbelinck (1959) demonstrated that upon the administration of alcohol mice showed an increased metabolic rate of 8 per cent when engaged in "heavy muscular exercise." However, the preponderance of evidence seems to indicate that the rate of oxidation is the same whether the subject is at rest or exercising. It is believed by some investigators that the rate of oxidation of alcohol in the tissues is a function of concentration. Here again the evidence is conflicting, yet it appears that over wide ranges of concentration the rate of oxidation remains fixed. For a given dose of alcohol the rate of metabolism appears to be more rapid immediately after equilibrium in the tissues is established (Jetter, 1938). The disappearance of the alcohol is slower thereafter. Marshall and Fritz (1953) demonstrated that the rate of oxidation of alcohol in the dog as measured by the blood level was fixed only at relatively high concentrations. At lower levels (2 to 8 mg. per cent) the rate of disappearance from the blood is a function of the concentration.

Newman and Cutting (1936) observed that the rate of metabolic disappearance of alcohol in the tolerant and nontolerant dog was approximately the same. Fleming and Stotz (1935) found that the disappearance rate of alcohol from the blood of habitués and nonhabitués was not significantly different. From the available evidence it appears that there is no significant difference between absorption, metabolism, and excretion of alcohol in the alcoholic and in the normal individual.

**Effect of drugs on the oxidation of alcohol.** Thyroxin does not accelerate the oxidation of alcohol in the body. The effect of thyroxin upon alcohol oxidation in Basedow's disease was negative (Lolli, 1937). It was shown however, by Newman and Smith (1959) and Goldberg *et al.* (1960) that triiodothyronine accelerated the metabolism in dogs and man. It was suggested that the effect was due to an enhancement of the activity of the hepatic enzymes concerned with the metabolism of alcohol. Neither epinephrine nor pituitrin affects the oxidation of alcohol in the tissues.

Insulin has been extensively studied with respect to alcohol oxidation. Studies in laboratory animals revealed little influence of insulin upon the rate of alcohol metabolism. In man, small doses of insulin behaved similarly. However, large doses of insulin appear to increase slightly the disappearance of alcohol from the tissues. Jacobsen (1952) reviewed this controversial subject and suggested that perhaps an explanation for the variability of results by different investigators can be found in the observations of Widmark (1935). He found that insulin increased the metabolism of alcohol in dogs with a low alcohol metabolic rate but failed to do so in animals with a high metabolic rate.

However, when insulin and glucose are administered simultaneously, alcohol often appears to be more rapidly oxidized. Apparently alcohol "burns in the flame" of rapidly metabolizing carbohydrate. Taylor and Gross (1940) administered insulin and glucose to a child who had drunk 200 ml. of "rubbing" alcohol. Upon admission the blood alcohol was 380 mg. per cent. Other restorative measures apparently were of no avail. Survival was accomplished by the simultaneous administration of glucose and insulin.

Dinitrophenol (Widmark, 1935) possesses the capacity of increasing the total metabolism of animals. Under the influence of dinitrophenol, alcohol also disappears more rapidly from the blood of dogs. Although undoubtedly some of the alcohol is lost by hyperventilation produced by dinitrophenol, much of the alcohol appears to be oxidized at an accelerated speed.

### THE PHARMACOLOGIC RESPONSE TO ALCOHOL

**The central nervous system.** The acute effect of alcohol on the central nervous system is limited to the brain. However, chronically it may produce myelitis, encephalitis, and polyneuritis. Quantities of 30 to 60 ml. exert their effect upon the ascending reticular formation and directly or indirectly upon the inhibitory centers in the cerebral cortex. The most usual manifestation of its action appears sequential to the depression of the inhibitory centers. In larger quantities the depressant action extends to the centers of respiration in the medulla. Alcohol kills by respiratory paralysis.

The depression of the cerebral inhibitory centers is manifested in a typical behavioral pattern. There is a freer play of elemental behavior. Speech is loud but frequently slurred. The subject may become very voluble and mistake his loquacity for eloquence. Self-criticism is diminished, and sensitivity to the criticism of others is often lost. This sense of freedom from inhibition and of false euphoria, with a freer play of the motivating instincts of life, has given alcohol the false reputation of being a stimulant.

Tasks which are dependent upon conditioned reflexes are not performed so well under the influence of alcohol. Pricking a moving target, target shooting, typing, and mountain climbing are all adversely affected by the ingestion of alcohol.

The work of Casper (1958) on the effect of alcohol on the ascending reticular formation in rats indicates that this system is markedly affected by alcohol. When alcohol was given in doses of 0.5 to 12 gm./kg., a prompt reduction in the spontaneous activity of the reticular formation was observed. The degree of inhibition was a function of the blood alcohol level. As the depression of the reticular activity progressed, there was at first a rise in the amplitude of the electrical activity of the cortex. It was only when the blood alcohol level approached that which evokes coma that the hyperexcitability of the cortex diminished to levels below the normal waking state. Casper's work indicates that the target cells for alcohol depressive action lie in some part of the ascending reticular formation. Carpenter *et al.* (1961) suggest that alcohol in small doses may improve performance in complex intellectual problems, possibly by inhibiting the alerting activity of the reticular system, thus shielding the person from distracting external sensations.

The effect of alcohol upon the sensory areas of the cortex extends to the motor areas as the concentration of alcohol in the blood increases. The following data correlate blood concentration of alcohol with effect on the central nervous system:

*Effect of Alcohol on the Brain*

*Stage 1.* 55 mg. per cent (30 to 50 ml.)
Querulous and a false euphoria
*Stage 2.* 100 to 200 mg. per cent (60 to 90 ml.)
Irregularity of gait
Lack of coordination of extremities
Mental confusion
*Stage 3.* 250 to 500 mg. per cent (150 to 300 ml.)
Respiratory depression—stupor and possibly death

The maximal effect of alcohol on the brain is during the time when the curve of blood concentration is in its ascendancy. The same concentrations of alcohol in the blood, *i.e.* 55 mg. per cent, in the first 15 minutes of a time-concentration curve may produce the effect of Stage 1. If the curve reaches 75 mg. per cent and descends, 55 mg. per cent concentration an hour later on the descendancy of the curve is likely to evoke no symptoms. It is while the cells of the reticular formation and the cortex are becoming acclimatized to the presence of alcohol that the maximal effect is experienced. Repeated impacts of alcohol upon these target cells produce tolerance. The habitual drinker can ingest, without any symptoms, quantities of alcohol that would actually daze the uninitiated individual.

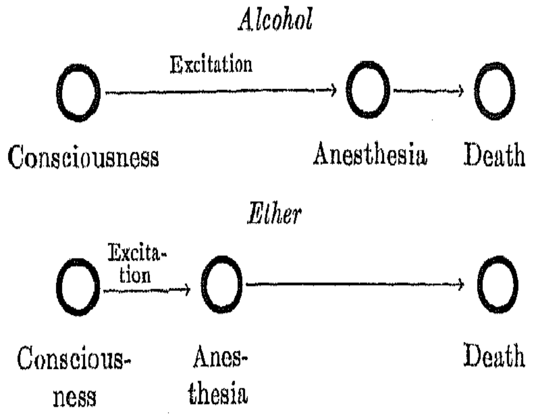
Lolli (1944) presented evidence to show that the depressant action of alcohol on the brain was associated with its capacity to produce partial cerebral dehydration. Furthermore, Himwich (1951) showed that cerebral metabolism *in vivo* was depressed by alcohol. Brain tissue is capable of oxidizing small concentrations of alcohol *in vitro*. It has been observed that small concentrations of ethanol added to slices of rat brain cortex increased their respiratory rate. Larger concentrations, however, depressed the tissue respiration. On the other hand, Sutherland *et al.* (1956) showed that ethanol did not affect the oxygen uptake of human cerebral cortex *in vitro* with any of the usual substrates. Ethanol was shown not to affect lactic acid accumulation with a glucose substrate, but reduced lactic acid accumulation with a pyruvate substrate. Wolpert *et al.* (1955) demonstrated that alcohol did not affect the oxidative phosphorylation of the mitochondrial fraction of rat's brain, as does ether. Rehak and Truitt (1958) observed that acetaldehyde in very low concentrations depressed the P/O ratio of rat brain mitochondria with pyruvate as a substrate. It is of interest that the depression of P/O ratio of brain mitochondria occurred in lower concentrations than prevailed with liver mitochondria. It is possible that this is one of the facets of the action of alcohol upon the brain. It is clear however, that the syndrome resulting from the presence of alcohol in the brain is a result of many factors.

Burbridge *et al.* (1959) showed that the rate of oxidation of alcohol in the brain and liver *in vitro* is not affected by its concentration. The metabolic pathways in the brain and liver appear to be different. Glucose substrate supported a greater uptake of alcohol by brain tissue than did any other substrates employed. Of special interest is their finding that the human brain, similar to the rat brain, showed a diminution of alcohol uptake in the presence of pyruvate and acetaldehyde. Rehak and Truitt (1958) found that the metabolic change produced by acetaldehyde in the presence of Antabuse was due to the coupling of the compound with a 2-carbon intermediate from pyruvate to form *acetoin*. In this manner, the energy production of the metabolic system is inhibited. The liver does not appear to use this pathway of acetaldehyde detoxification to the same degree as does the brain.

Lee (1962) demonstrated in rabbits that alcohol injected into the common carotid artery increased the permeability of the blood-brain barrier. Injected radioactive iodinated albumin did not cross the blood-brain barrier in normal rabbits. When alcohol was injected in quantities sufficient to produce an alcohol blood level of 200 mg. per cent, the cerebral vascular bed became permeable to the albumin and the compound appeared in the brain. Lee observed the peak penetration in 2 hours, with a disappearance of the increased permeability after 52 hours. However, even after 6 hours the effect was very weak. Lee favors the hypothesis that the effect of alcohol on the blood-brain barrier is sequential to its action on neuronal metabolism. He further suggests that blood levels of alcohol of 200 mg. per cent may render the brain vulnerable to substances such as bacterial toxins and neurotropic viruses that could not penetrate the barrier in a sober person.

Alcohol has a wide reputation as a respiratory stimulant in collapse. Is this justified? Indeed, the only direct effect of alcohol upon the respiratory centers is that of depression. However, when alcoholic beverages such as brandy and whisky are administered in collapse, they reflexly stimulate the respiratory centers. The presence of alcohol on the buccal, esophageal, and gastric mucosa causes local irritation. Receptors present in these membranes are connected by afferent fibers to the medulla. The irritation of these sensory nerve endings reflexly stimulates the medullary centers, particularly the centers of respiration. Whenever alcohol is employed as a reflex respiratory stimulant, brandy appears to be the beverage of choice. Its irritant action exceeds that of the other distilled beverages. It should be remembered further that overdosage will antagonize the local reflex action of the brandy by the central depressant action of alcohol.

Prior to the use of ether in anesthesia, alcoholic wines were frequently used to narcotize patients. The following diagram illustrates the unsuitability of alcohol as an anesthetic.



Alcohol provides an undesirably long period of excitation during induction. When anesthesia is reached, the patient is on the verge of respiratory collapse and death. The syndrome is quite different with ether, as indicated by the diagram above.

Individuals in an alcoholic stupor frequently succumb to severe shock. Apparently the impaired respiratory mechanism is unable to stand severe fright or traumatic injury. Such procedures as reducing a fracture in an inebriated person should be postponed until the alcoholic concentration of the blood is below the danger level.

McQuarrie and Fingl (1958) observed in mice that alcohol elicited anticonvulsive activity (raising the threshold to electroshock) only when administered in quantities that produce central nervous system depression. Upon administering alcohol repeatedly for several days and then abruptly withdrawing the alcohol, the threshold to seizure was lowered. These investigators interpret these studies as indicating physical dependence upon alcohol on repeated administration.

*Action on nerve trunks.* When alcohol (80 per cent by volume) is injected perineurally, a degeneration of the nerve trunk follows. Painful stimuli passing over the nerve are blocked. The effect of the injection of alcohol around a nerve may last for many months. The nerve later regenerates. There is a reorganization of the neurilemma and a proliferation of cell nuclei and protoplasm. The nerve trunk is restored to its normal integrity.

This treatment may be employed in trigeminal neuralgia; the alcohol is injected into the maxillary branch of the trigeminal nerve at the point of its exit through the foramen rotundum. The injection of the mandibular branch is made at its exit through the foramen ovale. It has been employed also in severe sciatica. The employment of alcohol to cause nerve degeneration is not without risk of interfering with the motor activity of a nerve trunk.

**The heart and circulation.** An analysis of the available data recording the effect of alcohol on the heart and circulation indicates that its action is not striking. Most of the effects observed in man and animals are minor and result from the primary action of alcohol on the brain. There is no crucial evidence to show that alcohol is a cardiac stimulant. Brooks (1910) and the authors (1945) showed that the infusion of weak alcoholic solutions slowly into the circulation of dogs and cats produced a progressive fall in blood pressure, cardiac slowing, and irregularities. Grollman (1942) gave 15 ml. of diluted alcohol to a total abstainer and measured various circulatory functions. His data are shown in figure 21-2.

It is observed that the effects are not striking and indeed may be the result only of the psychic stimulation. Larger doses of alcohol administered to an occasional drinker produced a 10 per cent increase in cardiac output, which appeared slowly and persisted for about 30 minutes. The blood pressure was slightly increased, which served to maintain the increased cutaneous circulation resulting from the vasodilatation produced by the alcohol.

Alcohol in moderate doses causes peripheral vasodilatation. There is a feeling of warmth on the skin and frequently reddening of the cheeks and nose. For this reason, alcohol is administered in vascular stasis as a result of exposure to cold. It would follow, therefore, that the alcohol should not be administered if the individual is to be further subjected to cold. This would tend to chill the peripheral blood. The results are most satisfactory after exposure, when the subject is brought into a warm environment.

Referring to the effects of alcohol in moderate amounts in the treatment of circulatory disturbances, Grollman (1942) states:

> "The apparent stimulating effect of alcohol in transient heart failure, syncope, or shock is probably to be attributed to the reflex stimulation induced in the mucous membranes of the gastrointestinal tract and comparable, therefore, to the effect observed with other irritants, such as smelling salts.

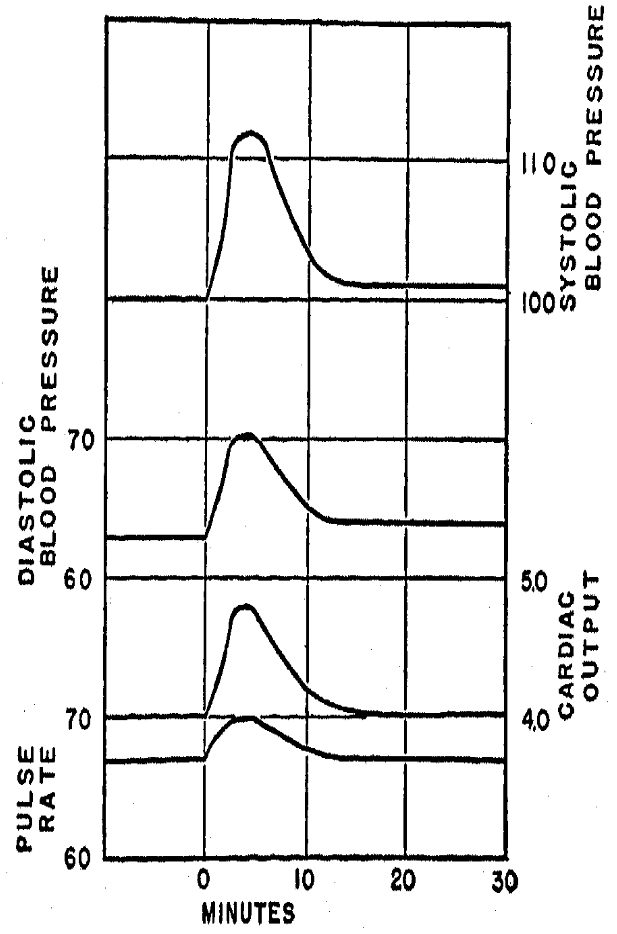


FIG. 21-2. The effect of the administration of 15 ml. of alcohol (as a 40 per cent aqueous solution) on various circulatory functions. The alcohol was administered at time indicated as 0 on the abscissa, the basal values being indicated to the *left* of this point. All values are expressed in terms of their conventional units. (From A. Grollman, Quant. J. Stud. Alc., 3: 5, 1942.)

> "The most valuable effect of alcohol on the circulation resides, probably, not in its direct effects on this system but rather in its capacity to allay anxiety and worry. By removing nervous inhibitions and excitability, it exerts a mildly narcotic effect which secondarily may act as a sedative to the circulation."

The evidence in the literature appears to support this view.

Whether or not the coronary arteries share in the peripheral vasodilating action of alcohol has been the subject of many investigations. Lasker *et al.* (1955) used the open-chest anesthetized dog to study the problem. They found that the rapid intravenous administration of alcohol caused increases in coronary flow as high as 100 per cent at an alcohol blood level of 149 mg. per cent. However, when the drug was given slowly and blood levels varied from 42 to 92 mg. per cent, the increases in coronary flow averaged 30 per cent. In their experiments papaverine and aminophylline were found to be superior to alcohol as coronary dilators. In extrapolating these results to man, one must be always mindful of the fact that the analgesic effect of alcohol may mask the pain of cardiac ischemia and thus give the anginal or postcoronary patient a false sense of security.

The effect of alcohol upon atherosclerosis has been studied repeatedly, and the problem is the subject of much controversy. Nikkila and Ollila (1959) studied the effect of the ingestion of a 7 per cent alcohol solution (used as drinking water) in 173 cockerels. Atherosclerosis was induced by cholesterol feeding. They were not able to demonstrate any protective effect evoked by alcohol against the atherosclerosis-inducing effect of hypercholesteremia.

Gimeno *et al.* (1962) showed that alcohol levels between 110 and 880 mg. per cent depressed the activity of the rat atria. The effect varied linearly with the concentration of alcohol. Shortening of the action potential, with a simultaneous decrease in contractility, appeared to be the most characteristic change in the electrical properties of the tissue. The decrease in the duration of the action potential may predispose the atria to arrhythmias, such as ectopic beats and fibrillation.

Battery *et al.* (1953) studied the effect of alcohol on cerebral blood flow and metabolism in a series of individuals varying from 18 to 65 years of age. The alcohol was given intravenously or administered orally in the form of whisky. Cerebral blood flow was measured by the nitrous oxide method developed by Kety and Schmidt (1948). They found that concentrations of alcohol sufficient to produce facial vasodilatation and mild inebriation elicited no changes in *cerebral blood flow*, *cerebral metabolism*, or *cerebral vascular resistance*. Severe alcoholic intoxication diminished cerebral blood flow and cerebral metabolism. These studies indicate the futility of using alcohol in the treatment of patients with cerebral vascular disease.

**Body temperature.** Moderate quantities of alcohol produce no effect upon body temperature. When one is exposed to severe cold, the administration of 30 to 40 ml. of alcohol affects the heat center in the hypothalamus, effecting a fall in body temperature of 1½ to 2°F. Simultaneously, however, there is a subjective feeling of warmth resulting from the peripheral vasodilatation which alcohol elicits. The fall in body temperature is likely the result of both the central and peripheral actions of alcohol.

Alcohol in moderate quantities synergizes the action of antipyretic drugs such as the salicylates when these are administered to a hyperpyrexic individual.

**The gastrointestinal tract.** When administered prior to a meal, alcohol in moderate quantities produces a mild depression of inhibitions. This allays anxiety and sensations of fatigue, and the individual is better prepared to digest food than when tenseness exists.

In addition to the release from tension which alcohol produces, it is a mild irritant to the mucosa of the gastrointestinal tract. It therefore stimulates the flow of digestive juices. In fact, a 7 per cent alcoholic solution may be advantageously used as a test meal for the determination of gastric acidity. It should be remembered that when permitted in cases of hyperacidity alcohol has no buffering effect on gastric acid. Therefore, its use in peptic ulcer is interdicted.

Beazell and Ivy (1940) are of the opinion that this effect of alcohol is due to the liberation of a histamine-like substance or perhaps gastrin on the gastric mucosa. Experiments with isolated portions of the stomach and duodenum demonstrated that only the antrum of the stomach and the duodenum exhibit this response to alcohol. Concentrations of alcohol above 15 to 20 per cent inhibit gastric secretion and may cause marked inflammation. Vomiting may occur after

rapidly drinking beverages of high alcoholic content. Newman (1954) demonstrated that emesis may occur if the alcohol is given intravenously and the alcoholic blood level reaches 120 mg. per cent. This would seem to indicate that the emetic effect of alcohol has a central as well as a peripheral component.

In addition to the stimulating effect of moderate amounts of alcohol on the appetite, the presence of bitters, tannins, and esters in alcoholic beverages synergize its action. These substances serve as simple bitters and tend to stimulate the appetite.

Goetzl and his associates (1950) carried out experiments to determine the effect of ingested alcohol upon olfactory acuity and the sensation complex of appetite and satiety. They showed that the ingestion of 75 ml. of 12 per cent alcohol is capable of producing a decrease in olfactory acuity and a conversion of appetite into satiety. It appears to be well established that in certain individuals the ingestion of too strong a drink or of too many drinks may cause their desire for the forthcoming meal to diminish or even to vanish. However, our observation indicates that in most people mild alcoholic beverages before meals have a benign influence on the appetite in spite of the effect of alcohol upon the olfactory acuity.

The chronic effect of large, repetitious quantities of alcohol on the gastric and intestinal mucosa in most cases is definitely injurious. Large quantities of alcohol impede the action of digestive enzymes. Chronic gastritis and gastroenteritis often result. The mucosa becomes indurated, and its capacity to absorb other foodstuffs is reduced. The chronic alcoholic is frequently a chronic dyspeptic. The lack of absorption of a varied diet from the tract frequently results in an avitaminosis. This is especially true in the case of thiamine. The deficiency of this vitamin in the tissues of the dipsomaniac appears to be one of the contributing factors in the production of delirium tremens.

Although evidence incriminating alcohol in chronic gastritis remains polemic, it appears from the studies of Lucas and Gillespie (1961) that in the rat and in man damage caused to the mucosa by a single intoxicating dose of alcohol is minimal.

The deleterious effect of alcohol on the normal digestive processes allows putrefactive changes to occur in foodstuffs in the alimentary tract. These substances are absorbed and repeatedly impinge upon the liver. This is believed to be one of the primary causes of so-called alcoholic cirrhosis.

**The skin.** Alcohol (95 per cent) has a cooling but dehydrating action when applied to the intact skin. The most suitable concentration of alcohol for external application is 70 per cent. This concentration is no longer dehydrating. Because of its low boiling point, alcohol evaporates readily from the skin, reducing the skin temperature and producing a pleasant sensation of coolness.

Alcohol dissolves the sebum from the skin and thus is an excellent solvent for germicides that are used locally. It has a low surface tension and therefore penetrates interstices and spreads well over surfaces.

Rubbing with alcohol is beneficial in reducing the incidence of bed sores (decubitus) during a protracted illness. The mechanism of the action of alcohol in this capacity is not understood. It is an excellent lubricant for skin massage. Its use stimulates circulation and produces an agreeable psychic response.

Owing to the high cost of alcohol because of the excise tax, isopropyl alcohol has been employed for rubbing purposes. Its odor is less acceptable than that of alcohol. However, its germicidal value is slightly greater than that of alcohol.

*Effect on bacteria.* Alcohol is widely employed locally because of its germicidal power. Numerous tests have shown that 70 per cent alcohol is more effective in this capacity than undiluted alcohol. This appears to be due to the better penetrating power of 70 per cent alcohol into the bacterial cell. Undiluted alcohol coagulates the peripheral cytoplasm, which thwarts its further penetration.

Alcohol removes the sebaceous layer from the skin prior to parenteral medication. It cannot be relied upon to kill bacterial spores, however. The cleansing power of alcohol is excellent, but as a germicide it cannot be depended upon.

For insulin and other repeated injections isopropyl alcohol, or a mixture of alcohol and isopropyl alcohol, is a more reliable germicide than alcohol.

### Social Aspects of Alcohol

The American public spends over 12 billion dollars a year on alcoholic beverages. The total Federal, state, and local taxes on this *expenditure* are over 3.3 billion dollars. Over 212 million gallons of distilled spirits were produced for consumption in 1962, a per capita consumption of about 1.2 gallons: consumption of wine was about 0.75 gallon and of beer, about 14 gallons.

Social drinking is engaged in by over 70 million people in the United States. They use alcohol. But another million chronic alcoholics are used by alcohol. The latter group provides one of the major social and medical problems of the United States. Alcoholism is a sociologic problem in which medicine has a vital interest, for alcohol is a drug.

The organization of such groups as the Rutgers Center of Alcohol Studies, Alcoholics Anonymous, and the National Council on Alcoholism, and the establishment of divisions of alcoholic hygiene in many state health departments show public consciousness of this problem. The publication of the *Quarterly Journal of Studies on Alcohol* is another indication of the public and scientific awareness of the urgency of the alcohol problem.

**Social drinking: why do people drink?** Drinking is a favorite social custom. In certain societies it is unsociable not to drink, and the conformist feels constrained to "when in Rome do as the Romans do." Drinking breaks down social restraint. It is often said, "I am at my best after two highballs." Self-criticism, shyness, and apprehension are dismissed. Drinking permits one to escape from the realities of life. It enables one to get out of his own company for a time. It permits one to face life temporarily on a more or less subcortical level. Many people like to do this. To the moderate drinker alcohol makes reality more pleasurable, minimizes irritations, smoothes off rough edges, and "knits up the ravelled sleave of care." These and many other social and psychic factors contribute to an explanation of why people drink.

*Moderate drinking and the automobile.* The greatest difficulty that one finds with social drinking is that every alcoholic is an unsuccessful social drinker. But even social drinking has many very adverse effects upon society. Among these are the lowering of moral standards, the disregard for the property of others, and the operation of a motor vehicle after drinking.

Holcomb (1938), of the Traffic Institute of Northwestern University, made an interesting study of the relationship of drinking to traffic accidents. In the vicinity of Chicago (this has been confirmed in other cities) from 10 to 15 per cent of the people operating motor vehicles had been drinking. Two per cent had more than 100 mg. per cent of alcohol in their blood. Nearly one-half of all the automobile operators involved in accidents had alcohol in their blood. Later this was confirmed by Gettler in New York City.

Among the automobile operators having alcohol in their blood, Holcomb found 2 per cent at noon and 16 per cent at midnight. The age peak was 25 to 30 years, with no difference between the sexes. The time peak was between 10 p.m. Saturday night and 2 a.m. Sunday morning.

Studies by Bjerver and Goldberg (1950) in the Caroline Institute in Stockholm are germane to the problem of alcohol and traffic accidents. Their subjects were experienced drivers. They each were given from 1 to 1.3 liters of beer or 100 to 130 ml. of brandy. They were then given driving tests such as weaving through obstacles, rapid starting and stopping, and backing. On the average the subjects had 50 mg. per cent alcohol in their blood. There was a deterioration in driving performance of 25 to 30 per cent when compared with the skill of a controlled group of drivers who had not imbibed. The threshold blood alcohol concentrations for impairment of performance of expert drivers was found to be between 35 and 40 mg. per cent. This concentration of alcohol in the blood also caused these individuals to show a deterioration of their "flicker fusion" abilities and depression of their sensitivity to the "blink test."

Loomis and West (1958) observed that blood alcohol levels of 150 mg. per cent impaired the ability of subjects to drive by approximately two-thirds, as measured by a simulated driving apparatus. All subjects tested showed some deterioration of their driving ability at blood levels of 50 mg. per cent. These data indicate that alcohol probably plays a greater role as a causative agent in traffic accidents than is often admitted.

Hadden and Bradess (1959) surveyed the effect of alcohol in fatal automobile accidents involving drivers and pedestrians. Approximately 50 per cent of 83 persons showed blood alcohol levels of 0.15 per cent or more. An additional 20 per cent had blood alcohol levels of 0.05 to 0.15 per cent. These data from Westchester County, New York, correlate well with the findings from other sections of the United States and indicate the appalling fact that alcohol is strongly implicated in 50 per cent of the deaths resulting from motor vehicle accidents.

The tests for driving performance under the influence of alcohol conducted in Manchester, England, are of special significance. The ability of experienced drivers of double deck buses, under the influence of varying quantities of alcohol, to drive through a gap between two posts, leaving about a centimeter on either side, was studied. The alcohol did not disrupt their performance as much as it distorted their judgment of their performance. The difference between the narrowest gap between the posts at which they believed they would always succeed in driving and the narrowest gap at which they did succeed increased with the alcoholic intake. It is emphasized by these workers that alcohol causes a deterioration of the relationship between what one thinks he can do and his actual limit of performance. Accidents on the highway by drivers under the influence of alcohol are likely to be due to defective judgment related to skill, rather than to a deterioration of skill.

Approximately 32 people are killed every day in the United States as a result of drinking drivers and pedestrians. Each day 1000 people are killed by automobile accidents on the highways of the world, and for each death there are at least 50 nonfatal injuries. Data from a variety of sources indicate that from 20 to 50 per cent of these casualties are due to the effects of alcohol on the driver and/or the pedestrian (Cohen, 1962). There is only one rule. *Never drive after drinking.* The physician who practices this rule and suggests it to his patients will do much to solve one of our vital alcohol problems.

The effect of the ingestion of alcohol can be properly evaluated only from the viewpoint of the total situation of one's environment and the whole individual. In the early days of the development of our country, our society was person-oriented and largely individualistic. Drinking affected the person and his close associates. But in a complex integrated society, such as has existed since the industrial revolution, drinking often precipitates a *crisis situation.* When one adds to the automobile the railroad, the airplane, the motor boat, and the complex and gigantic tools of industry, one immediately sees the incompatibility of excessive drinking in an industrialized community. It may be added further that excessive drinking is incompatible with the democratic form of government because it has the capacity to impair the judgment of the individual.

*Tests for drunkenness.* The penalties for crime under the influence of alcohol are often different from those for one in command of normal faculties. This is particularly so with the operator of an automobile who is involved in an accident. Therefore it became incumbent upon medical science to develop methods to establish the state of "legal drunkenness."

Most enforcement authorities agree that from 100 mg. to 250 mg. per cent of alcohol in the blood constitutes being "legally drunk." There are many tests of a psychological character which one can apply to determine the actual impairment of mental activity by this rather high concentration of alcohol. Nevertheless reliance is generally placed upon the presence of the specific concentration of the alcohol in the blood. The chronic alcoholic may function reasonably well with this concentration of alcohol in the blood, whereas the uninitiated individual might be in an alcoholic stupor. Besides, there is great variation in the tolerance to alcohol by the cells of the cerebral cortex in different individuals. At present there is no adequate explanation for this personal variation, although many attempts have been made to segregate the groups of alcohol-tolerant and nontolerant persons.

The data of Harger and Hulpieu (1956) illustrate the individual variation of the effects of alcohol. Of a total of 5850 test subjects, the following proportions at each blood level were diagnosed as drunk: 10 per cent at levels of 50 mg. per cent; 34 per cent at levels of 51 to 100 mg. per cent; 64 per cent at levels of 101 to 150 mg. per cent; 86 per cent at levels of 151 to 200 mg. per cent; 96 per cent at levels of 201 to 250 mg. per cent; and 99 per cent at levels greater than 250 mg. per cent.

The methods of determining alcohol in the blood are dependable and relatively specific. The methods are now micro in character and can be carried out with the ease of a micro blood sugar determination. Essentially they depend upon the removal of the alcohol from the blood by volatilization. The alcohol is then oxidized by a standard solution of potassium dichromate, and the residual dichromate is determined after reaction with potassium iodide by titration with standard sodium thiosulfate.

In the absence of facilities for obtaining blood, a urine sample may be used. An analysis of the urine gives only a rough approximation of the blood alcohol. Some authorities hold that the concentration in the urine is 3 times that in the venous blood.

Another procedure is to collect a sample of expired air. In it alcohol may be determined by its capacity to reduce potassium permanganate. As a first approximation the quantity in the exhaled air is 1/2100 the concentration in blood (Holcomb, 1938). It is upon this principle that the determination of alcohol in the expired air by means of the "Drunkometer" depends. Another instrument used for the purpose of determining the alcoholic content of expired air is the Alcometer, developed by Greenberg and Keator. Its principle of operation depends upon the reduction of iodine pentoxide by alcohol to elementary iodine. The intensity of the blue color of iodized starch produced by the action of the iodine on starch solution is determined photoelectrically. The procedure is essentially automatic, and the results have been accepted as legal evidence by many courts.

Specificity and sensitivity are two highly important attributes which have been lacking in previous technics for the determination of ethanol. Lundquist (1959) was unable to find a single analytic method specific for ethanol. Gas-liquid chromatography offers a number of advantages that are not achieved in the older analytic methods for ethanol. These include rapidity, quantitative reliability, and specificity. Recently several methods have been published which utilized gas chromatography for the analysis of ethanol (Parker *et al.*, 1962; Duritz and Truitt, 1964). The latter method utilizes air samples which have been equilibrated with blood, rather than the blood itself. The employment of the air sample avoids much of the contamination of the gas chromatograph that would be encountered if blood were injected directly into the apparatus.

**Alcohol and crime.** Crime and alcohol are inextricably interwoven. This statement involves the moderate drinker as well as the dipsomaniac. To be sure, no one can say by way of a generalization that alcohol precedes crime or vice versa. Nevertheless, the following relationships hold with a fidelity that seldom wavers:

1. Crime is often planned in the place where alcohol is sold.
2. The tavern is the place where the criminal seeks his accomplices.
3. The criminal is seldom courageous and uses alcohol to depress his inhibitions and allay his fears.
4. The spoils of crime often are divided in the tavern.
5. Alcohol permits the criminal to rationalize his crime and relieves him of self-criticism.

Seneca, the Roman philosopher, wrote: "Drunkenness kindles and discloses every kind of vice, and removes the sense of shame that veils our undertakings. For more men abstain from forbidden actions because they are ashamed of sinning than because their inclinations are good."

The data compiled by Fisher are convincing with regard to the influence of alcohol on crime in the state of Maryland (see table 21-1).

**Alcohol as an aphrodisiac.** Alcohol has a reputation of being the "life of a party." It is bottled mirth and hilarity. It is believed by many to serve as an aphrodisiac. The facts contradict this.

Alcohol diminishes the strength of one's moral inhibitions. Established moral barriers are frequently broken. Religious teachings and marital obligations assume lesser significance under the influence of the drug. The individual achieves a rapid flight back through the centuries and becomes the "Old Savage in a New Civilization." All of this is misinterpreted as a stimulation of one's libido.

On laboratory animals, where psychologic influences do not play a role, the administration of alcohol diminishes sexual activity. Teitelbaum and Gantt (1958) administered quantities of 1 to 3 ml./kg. of alcohol to male dogs. These doses inhibited sexual reflexes as well as ejaculation. There was also suggestive evidence of sperm count diminution.

In man there is no evidence to show that alcohol increases one's libido or provokes erection of the penis. The effect of alcohol as an aphrodisiac is aptly stated by Shakespeare in *Macbeth*. The porter is speaking to MacDuff: "It provokes the desire, but it takes away the performance."

**Alcohol, longevity, and posterity.** There is no crucial evidence to show that alcohol taken in moderate amounts affects longevity or posterity favorably or adversely. The abuse of alcohol reduces the life span. The chronic alcoholic falls easy prey to infectious diseases such as pneumonia. His illness of alcoholism may be complicated with malnutrition and venereal disease; therefore the direct effect of alcohol alone is difficult to evaluate. Besides, the number of social and economic factors involved befog the critical evaluation of the data.

TABLE 21-1

*Incidence of Alcoholism in Homicides, Baltimore City, 1961*

| Manner of Homicide | Total Number of Cases | Per Cent Alcohol Content of Brain, Spinal Fluid, or Blood | | | | | |
|---|---|---|---|---|---|---|---|
| | | Negative | 0.01–0.04 | 0.05–0.14 | 0.15–0.24 | 0.25–0.39 | 0.40 and above |
| Firearms | | | | | | | |
| Colored males | 18 | 6 | 1 | 4 | 5 | 2 | |
| Colored females | 4 | 3 | | | 1 | | |
| White males | 11 | 6 | | 2 | 3 | | |
| Sharp instruments | | | | | | | |
| Colored males | 14 | 1 | 1 | 2 | 9 | 1 | |
| Colored females | 3 | | 1 | 1 | 1 | | |
| White males | 5 | 1 | | 2 | 2 | | |
| Blunt force | | | | | | | |
| Colored males | 3 | 1 | | 1 | | 1 | |
| White males | 1 | 1 | | | | | |
| White females | 2 | 1 | | | | | 1 |
| Altercation | | | | | | | |
| Colored males | 3 | 2 | | | 1 | | |
| Colored females | 2 | 1 | | 1 | | | |
| White males | 1 | | | | | 1 | |
| White females | 2 | 1 | | | 1 | | |
| Total | 69 | 24 | 3 | 13 | 23 | 5 | 1 |

### The Chronic Alcoholic

The World Health Organization defines an alcoholic as "one who begins to be concerned about how activities might interfere with his drinking instead of how drinking might interfere with his activities." Drinking usually moves the alcoholic out of one of the traffic lanes of life—his family, his business, or his social environment.

The alcoholic is a sick person. He deserves sympathy and understanding as much as does an individual with a chronic heart ailment. According to a recent report of the Metropolitan Life Insurance Company, there are in the United States 50 per cent more sufferers from alcoholism than from tuberculosis. The same source estimates that 4 million people in this country are either actual or potential alcoholics. Alcoholism accounts for approximately 19 per cent of the absenteeism in major industrial employment.

It is very difficult to estimate the number of alcoholics in any society. The number in the United States has been computed to be about 1 million. Obviously, the incidence will depend upon the definition of an alcoholic and also upon the adjustment to alcoholism which the individual has been able to achieve. It does appear that most estimates which have been made consider only the overt habitués of the "skid rows." The physician should be aware, however, of another group of alcoholics which have been designated as *hidden alcoholics*. These are the individuals who drink surreptitiously and manage to keep their habituation secret. Many of these people enjoy occupational stability and some are engaged in top-level positions. O'Hollaren and Wellman (1958) estimate that only 6 per cent of the alcoholic population is receiving treatment for the disease as such. Owing to the popular misconception of the typical alcoholic, physicians may fail to recognize alcoholism as the underlying cause of emotional and physical symptoms. Where hidden alcoholism is suspected, the physician should check the patient's history with the spouse or others closely associated with him.

The alcoholic pattern of excessive dependent drinking may develop from *genogenic* or *psychogenic* personality and metabolic maladjustments, from major psychiatric illnesses, from major psycho-neurotic reactions, from emotionally immature personalities reacting to life's responsibilities and strains, and from social drinking and heavy social drinking over a period of years. Alcohol may also be used, consciously or unconsciously, to allay anxiety and as a psychic or pharmacologic analgesic. In some, alcoholism is also considered evidence of latent or overt homosexuality and as evidence of deep unconscious self-destructive tendencies.

The personality of the alcoholic is often characterized by a poor frustration tolerance, basic anxiety defense reaction, and narcissism. He uses alcohol as an escape mechanism to hide from problems which are real and frustrating to him when he is sober. When treated and taken off alcohol, he hopes to achieve the capacity of becoming a social drinker again, for drinking has become so much a part of his social activity that he feels stigmatized if he cannot drink. Alcoholism, like schizophrenia, may be a surface syndrome in which a superficial similarity among alcoholics effectively obscures diverse etiologies. A detailed description of the alcoholic personality is presented by Korman and Stubblefield (1961).

**The liver of the chronic alcoholic.** The effect on the liver of drinking excessive quantities of alcohol has been the subject of many studies and much controversy. The issue is seldom clear cut; such factors as dietary and vitamin deficiency, infection, and a malfunctioning digestive system often befog the incrimination of alcohol as a prime factor in the pathogenesis of Lanënec's cirrhosis. The fact that alcohol is metabolized principally in the liver does not preclude the possibility of damage to the organ resulting from the repetitious catabolism of large quantities of alcohol. It has been demonstrated that alcohol inhibits certain enzyme systems in the liver. Seligson *et al.* (1958) has shown that alcohol may reduce the activity of the citric acid cycle in the liver. He suggests that this may reduce the amount of available adenosine triphosphate and thus inhibit the enzyme systems dependent upon ATP; extended for prolonged periods, this could result in cellular damage. Henley *et al.* (1956) demonstrated that alcohol inhibited liver glutamic pyruvic transaminase. The effect of the inhibition of this enzyme system upon the cellular structure and function of the liver has not been determined. It appears, therefore, that although malnutrition and other factors associated with heavy drinking play a role in the production of liver damage, the ultimate effect of alcohol alone has not been completely explored. Its primary effect may be brought about through mechanisms which as yet have not been identified (Klatskin, 1959).

Gillespie and Lucas (1961) presented evidence to show that feeding rats nonintoxicating levels of alcohol evoked hepatic lesions. The dietary intake was hypolipotropic. The lesions were due to choline deficiency. In other studies these workers showed that one intoxicating dose of alcohol in rats will produce a hepatotoxic effect, as shown by the presence of slightly more extractable lipids. These results were confirmed by Kutob and Plaa (1962), who showed that alcohol enhanced the hepatic toxicity of chloroform in rats. They found an increased level of lipids in the liver, which was responsible for a higher chloroform retention by that organ.

**Treatment of acute drunkenness.** Seliger suggested the following steps in the treatment of acute drunkenness:

1. Remove the liquor from the patient.
2. Get the alcohol out of his stomach and tissues.
3. Administer fluids and food to assist in restoration of water balance, vitamins, and salts. For this purpose 1 to 2 l. of 10 per cent dextrose in isotonic salt solution is injected slowly intravenously. To this fluid is added 25 units of insulin and 100 to 200 mg. of thiamine hydrochloride.
4. Goldberg *et al.* (1960) used intravenous injections of triiodothyronine to reduce the blood levels of alcohol in acutely intoxicated persons. They injected a total dosage of 200 mcg. of the hormone and increased the disappearance rate of blood alcohol from 15 mg./100 ml./hr. to 32.1 mg./100 ml./hr. The sobering effect of the accelerated rate of alcohol metabolism occurred in 2 hours, as compared to 6 to 10 hours in untreated individuals.
5. Administer sedatives when indicated. For the purpose of sedation, 60 to 120 mg. of phenobarbital is administered. As an anticonvulsant, 180 mg. of diphenylhydantoin sodium may be desirable. Phenobarbital may be continued, 60 mg. 3 times a day for several days.

6. Protect the patient so that he cannot injure himself or others. See also treatment of delirium tremens (below).

**Treatment of the chronic alcoholic.** The treatment of the chronic alcoholic may be divided under 3 headings.

1. Drug therapy
2. Nutritional therapy
3. Psychotherapy

Thiamine hydrochloride, 100 to 300 mg. intravenously, is indicated. The barbiturates such as pentobarbital sodium, 0.1 gm. to 0.2 gm. at bedtime, may be used for insomnia. Diphenylhydantoin sodium, 0.1 to 0.2 gm., is used also to combat convulsive seizures. Dexedrine sulfate, 5 to 50 mg. 3 times a day, may be used in excessively depressed alcoholics.

Dietary measures are especially necessary in the malnourished alcoholic. The diet is general, with a high caloric intake supplemented by vitamins, especially thiamine hydrochloride. The chronic alcoholic usually shows a distorted electrolyte balance. For example Barlow and Wooten (1959) studied changes in the constituents of blood in 64 long-term alcoholics prior to treatment. They found that plasma $K^+$, $Na^+$, $Cl^-$, and red cell $Cl^-$ were reduced significantly. On the other hand the $K^+$ of the erythrocytes was elevated. The $Na^+$ of the erythrocytes remained unaltered. Plasma protein concentration and hematocrit values were found to be significantly lower than those of controls.

The psychotherapy of the chronic alcoholic is the most difficult of the 3 forms of the treatment. Essentially, the physician is dealing with a person with problems who uses alcohol to escape from them or uses the drug to narcotize himself against their poignancy. For an adequate discussion of this phase of treatment, the reader is referred to texts on psychiatry.

In the management of the chronic alcoholic the facilities of "Alcoholics Anonymous" appear to supply a definite need in treating and preventing relapse in some cases of alcoholism. The community of interest in a common problem has an excellent psychological effect. Their dependence upod a higher power than their own will has a benign influence. In many cases "Alcoholics Anonymous" provides an opportunity for the alcoholic to become part of the answer to his own problem.

The problem of psychotherapy for an individual has been most successful when extended to the spouse also. It is essential for the spouse to recognize the compulsive force of drinking in the alcoholic and assist in combating it. Frequently such cooperation is the means of salvaging a home which might otherwise be wrecked by alcoholism.

Miller (1959) used hypnosis to create an aversion to alcoholic beverages in 24 chronic alcoholics. The patients were made to relive their unpleasant hang-over experiences during the trance. Over a 9-month follow-up period success was achieved in 20 of 24 patients. This is an interesting approach to the problem of alcoholism and should be given a wider application, especially in those cases where the classical procedures have failed to produce favorable results.

*Delirium tremens.* Delirium tremens is a familiar alcoholic mental disease characterized by visual hallucinations (seeing many animals and faces actually not present), accompanied by marked fear of the objects seen, confusion, disorientation for time, place and, in general, being out of contact or 'off the beam.'

Studies of patients with delirium tremens, or the D.T.'s, reveal that they nearly always give a history of heavy drinking, eating very little, drinking more, and then not eating at all. Therefore nutritional depletion (especially of vitamin $B_1$) is a major factor in the production of this illness.

The following steps are suggested in the treatment of delirium tremens:

1. Withdraw alcohol abruptly.
2. Give 0.1 gm. each of phenobarbital and diphenylhydantoin sodium orally as a sedative and anticonvulsive.
3. Inject 1 to 2 l. of 10 per cent dextrose in normal salt solution intravenously.
4. Administer by slow intravenous drip 100 to 200 mg. of thiamine hydrochloride and 25 units of insulin.
5. One and one-half hours later repeat the sedatives in (2).
6. In refractory cases the insulin and dextrose and thiamine hydrochloride may be given again on the second day.
7. The sedatives may be continued for several days 3 times daily. Thiamine hydrochloride may be given orally also.
8. Many of the psychotropic drugs are used in the treatment of alcoholism. Chlorpromazine (Albert *et al.*, 1954), promazine (Mitchell, 1956), and meprobamate (Greenberg *et al.*, 1957) have been used with varying degrees of success. When the

phenothiazine derivatives are employed, one must be aware of the hypotension that may result from the synergism of these drugs with alcohol or other drugs of a sedative nature that might have been previously administered. These agents provide relief from the anxiety that forces the patient to drink. Mooney *et al.* (1961) in a double blind study found chlordiazepoxide to be the most satisfactory in a comparison with other psychotropic drugs. His criterion for success was based upon the patient's not discontinuing the therapy; therefore the "return rate" of patients was used as an index of the effectiveness of the therapy. It is important to determine the underlying cause of the patient's anxiety and to gradually reduce the dosage of the psychotropic drug used in the more acute phases of treatment. Habituation to the psychotropic drug must be avoided.

In the depressions that frequently are associated with the withdrawal of alcohol, amphetamine has been used with success to elevate the patient's mood. Other antidepressants (see page 479) have been used also for this purpose (Lawrence *et al.*, 1960).

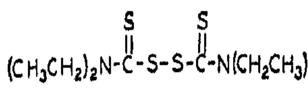
9. When sedation fails to produce in the patient the tranquilized state which is sought, the corticotropic hormone ACTH (see page 832) is indicated. Fischback *et al.* (1952) used 25 mg. of the hormone intravenously, slowly infused in 1 L. of 5 per cent glucose solution. Recovery with this therapy may be dramatic. This finding points to the possibility of alcoholism being a metabolic disturbance.

McAllister (1952) states: "It (adrenal cortical extract) should be combined with the recognized treatment of the alcoholic, such as psychotherapy and rehabilitation."

The adrenal cortical hormone approach is valid and apparently is one method of aiding in eliminating the drying-out period in acute alcoholism and lessening the recurrent craving for alcohol in certain people.

10. Give individual psychotherapy according to the needs of the patient. The rehabilitation of the patient requires various forms of psychotherapy. It is a generally accepted dictum that total abstinence is essential for the successful treatment of the alcoholic. However, Davies (1962) reported about 8 per cent of 93 cases of former alcoholics who had successfully adjusted to social drinking. Nevertheless, he warns the aim should be total abstinence.

**Disulfiram (Antabuse) in the treatment of alcoholism.** Antabuse is tetraethylthiuramdisulfide, as shown by the formula below.



$$(CH_3CH_2)_2N-\overset{\overset{S}{\|}}{C}-S-S-\overset{\overset{S}{\|}}{C}-N(CH_2CH_3)_2$$

Tetraethylthiuramdisulfide
Antabuse

The substance occurs as colorless or slightly yellow crystals which are nearly insoluble in water. In 1914. Koelsch described the effect of poisoning with cyanamide in workers who were exposed to this chemical. The symptoms observed were transitory flushing of the face, headache, accelerated pulse and deepened respiration, tachycardia hypotension, gastric distress, and vertigo. It was observed that these attacks occurred only after the ingestion of alcohol. Other substances in addition to cyanamide were observed to sensitize the organism to alcohol. Substances present in the fungus *Coprinus atramentarius* appear to produce the same type of sensitization. Hald *et al.* (1948) added a third substance, Antabuse, and introduced it into therapeutics as a drug in the treatment of alcoholism. Moench (1950) observed a sensitivity reaction to alcohol in persons who had previously ingested animal charcoal. Clark and Hulpieu (1958) confirmed this observation and found that the mechanism of action of animal charcoal was similar to that of Antabuse. Individuals became alcohol-sensitive upon the ingestion of 9 gm. daily of animal charcoal for 7 days. The action is not due to the charcoal *per se* but to a heat-stable, water-insoluble constituent.

Other substances have been reported to cause the anti-alcohol reaction when taken in conjunction with alcohol. These include the hypoglycemic drugs—tolbutamide, chlorpropamide, and phenformin (Truitt *et al.*, 1962).

Hald and Jacobsen (1948) were studying the effect of Antabuse on intestinal worms in rabbits. They tried the compound on themselves to test its availability for use in man. Coincidentally, each investigator drank a couple of cocktails, and each experienced severe gastrointestinal distress. They compared their symptoms and decided that these were not due to Antabuse alone but were due to Antabuse plus alcohol.

Antabuse appears to be relatively nontoxic. The lethal dose in animals reported by Hanzlik and Irvine (1921) was in the order of 3 gm./kg. Hald and Jacobsen (1948) gave individuals as much as 6 gm. daily and 0.25 to 0.60 gm. daily for several months without producing symptoms except upon the ingestion of alcohol. About 20 per cent of Antabuse is excreted in the feces; the remainder after absorption is slowly excreted by the kidney in the urine. Antabuse is slowly excreted, and the Antabuse-alcohol syndrome may be induced upon the ingestion of alcohol as long as 3 weeks after the drug has been stopped.

The symptoms produced by alcohol in the individual sensitized by Antabuse have been explained on the basis of the rapid oxidation of alcohol to acetaldehyde. Small quantities of acetaldehyde appear in the blood of normal persons who ingest alcohol. In the person sensitized by Antabuse, however, this concentration rises 2 to 5 times with the same dose of alcohol. For example, within 30 minutes of the ingestion of 40 ml. of gin a person will show a blood acetaldehyde concentration of 250 mcg./100 ml. After Antabuse and gin the concentration rose to 520 mcg./100 ml. Indeed Hine *et al.* (1952) found concentrations of acetaldehyde in blood of 1000 mcg. per cent in certain patients after the Antabuse-alcohol syndrome. The concentration of alcohol in the blood causing the reaction is exceedingly small. As little as 5 to 10 mg. per cent precipitate the syndrome. The fully developed effect occurs at blood levels of 50 mg. per cent alcohol, and unconsciousness is likely to prevail if the alcoholic blood level reaches 125 to 150 mg. per cent. It appears likely that Antabuse inhibits the enzyme system responsible for the conversion of acetaldehyde to acetate and thus permits quantities of acetaldehyde to accumulate in the tissues.

The question whether or not acetaldehyde actually accumulates and is the cause of the anti-alcohol reaction is controversial. Using a gas chromatographic method, Duritz and Truitt (1964) were able to prove definitely that acetaldehyde does accumulate when ethanol is given to Antabuse-pretreated animals. From the evidence it appears that acetaldehyde or some addition product of acetaldehyde with a tissue metabolite is responsible for the anti-alcohol reaction.

In experiments with rats' livers it has been shown that Antabuse inhibits certain enzymes, notably xanthine oxidase and succinoxidase. More recent investigations reveal that it also possesses an antithyroid action attributable to the presence of the -NCS grouping common to many antithyroid compounds. The mechanism of this action appears to involve interference with the iodine-trapping function of the thyroid gland, inasmuch as free iodine reacts with the drug *in vitro* to form a presumably stable, complex substance.

There are many cases in which Antabuse has produced such violent reactions when alcohol is ingested that death has followed. Becker and Sugarman (1952) reported a case of an apparently normal individual in middle life who died from the Antabuse-alcohol syndrome. This occurred from the ingestion of 1 oz. of whisky in the demonstration or test period. Leibetseder (1952) observed acute thrombocytopenic purpura following a 1-month course of Antabuse therapy. Busse *et al.* (1952) observed individuals with questionable normal electroencephalograms; after 2 weeks of Antabuse therapy, they showed distinctly dysrhythmic EEG patterns. These investigators suggest that hidden foci in the EEG pattern became apparent during Antabuse therapy.

Acetaldehyde has been shown to increase ventilation and heart rate, flushing of the face, and possible vertigo. It appears, therefore, that the Antabuse-alcohol syndrome is partially the result of acetaldehyde formation in the body from the ingested alcohol. The intravenous injection of acetaldehyde is accompanied by epinephrine release and hypertension (Eade, 1959). In the Antabuse-alcohol syndrome hypotension occurs. Christensen (1951) suggested that Antabuse produces this fall in blood pressure and flushing by acting as an adrenergic blocking agent, thus reversing the circulatory response to epinephrine. Truitt *et al.* (1962) demonstrated that the anti-alcohol action of tolbutamide is similar to that of Antabuse in that blood acetaldehyde is increased. However, the vasodilator component of the reaction cannot be explained by a reversal of the vascular effects of liberated epinephrine through an adrenergic blocking action of tolbutamide. It appears to be due to a prolongation of a direct vasodilator component of the acetaldehyde action as a result of interference with its decomposition.

*Clinical use of Antabuse.* After a week of sobriety, with the patient in good physical condition, and with his consent and a full explanation, Antabuse treatment is instituted. The dose for each day is given in the morning. Usually 500 mg. (1 tablet) is given daily for a period of 2 to 3 weeks.

The patient may then be hospitalized and given an alcoholic beverage of his choice; usually 20 ml. of whisky will produce the typical syndrome. This experience under controlled conditions repels the individual from alcohol. These symptoms act as a reminder to the patient of what will happen if alcohol is again ingested. The alcohol test is usually omitted in patients over 50 years old. After the initial dosage, maintenance dosage ranges from 125 to 500 mg. daily.

Our knowledge of this drug is still in its infancy. About 20 per cent of the patients using the drug experience fatigability. It should not be used on patients in which the alcoholism is complicated with *diabetes*, *cardiac disease*, *pregnancy*, *goiter*, *epilepsy*, *cirrhosis of the liver*, or *nephritis*.

It appears that the drug may prove to have usefulness in a limited number of patients in whom psychotherapy and all other rehabilitation measures have failed. In these individuals, in our opinion, it should be employed with caution as a temporary aid in establishing the individual's voluntary resistance to the ingestion of alcoholic beverages. The act of taking the dose of Antabuse serves as a sort of daily rededication of the alcoholic to achieving his goal of abstinence.

De Generes (1954) very cogently stated his experience with Antabuse with army personnel: "It is not a panacea for alcoholism, but it is useful as an adjuvant in an integrated program of psychiatry."

Becker (1954) instructed patients on Antabuse therapy to carry an Antabuse identification card in order to avoid the administration of agents containing alcohol in the event the individual is taken ill. The individual is advised against the ingestion of cough remedies, paregoric, paraldehyde, and foods prepared in wines, or the use of rubbing alcohol and aftershave lotions.

**Temposil (citrated calcium carbimide).** Temposil is a compound which, like Antabuse, prevents the oxidation of acetaldehyde, formed from the ingestion of alcohol, to acetate, carbon dioxide, and water. It appears to offer certain advantages over Antabuse. For example, a single dose of 50 mg. will suffice to sensitize a person to alcohol within 1 hour. The drug is more quickly excreted or inactivated than Antabuse; in most individuals 50 mg. daily is sufficient, while others may require 100 mg. daily. Smith *et al.* (1957) found the Temposil-alcohol syndrome to resemble the Antabuse-alcohol syndrome in emulating an allergic type of response. However, it differed from the latter in that the hypotensive response often seen in the Antabuse-alcohol syndrome did not occur. They are of the opinion that vascular responses to acetaldehyde in the two syndromes are distinctly different.

In a series of alcoholics studied with Temposil therapy, Ferguson (1956), Smith *et al.* (1957), and Mitchell (1958) found the therapy comparatively devoid of adverse side effects. Of special interest is the absence of the lethargy, impotence, and abdominal discomfort encountered by a segment of the patients under treatment with Antabuse. Glatt (1959) observed the occurrence of side effects with Temposil therapy to be greater than reported by previous investigators. However, they were less severe and less frequent than with Antabuse.

### ALCOHOLIC BEVERAGES

When sugar solutions undergo fermentation, the reaction proceeds essentially according to the following equation:

$$C_6H_{12}O_6 \rightarrow 2CO_2 + 2C_2H_5OH$$

Many other substances are formed simultaneously with the alcohol and carbon dioxide. Among these are glycerin, succinic acid, and numerous higher molecular weight alcohols. The mixture of amyl, butyl, and propyl alcohols formed along with certain aldehydes and esters is called *fusel oil.* Fusel oil is strongly intoxicating and produces severe headache.

The fermentation of glucose solutions proceeds until the alcoholic content reaches about 14 per cent. Concentrations of alcohol higher than this inactivate yeast. Therefore, undistilled beverages contain less than 14 per cent of alcohol or are "fortified" by the addition of alcohol.

Numerous substances containing sugar or starch (which may be converted into sugar) are used in the manufacture of the various alcoholic liquors, all of which contain ethyl alcohol, as well as coloring matter, ethers, esters, and many other substances.

**Wines.** *White* and *red wines* are obtained by the fermentation of grape juice; the so-called *light wines* contain 12 per cent or less of alcohol; the *strong wines*, such as *port* and *sherry*, from 19 to 25 per cent of alcohol; if the grapes contain much sugar, only a portion of it is converted into alcohol, while another portion is left undecomposed; such wines are known as *sweet wines. Effervescent wines*, such as champagne, are bottled before the fermentation is complete; the carbonic acid is retained under pressure in solution in the liquid.

**Beer** is prepared by fermentation of germinated grain (generally barley), to which much water and some hops have been added; the active principle of hops is *lupulin*, which confers on the beer a pleasant, bitter flavor. *Light beers* have from 2 to 4 per cent alcohol; *strong beers*, as *porter* or *stout*, from 4 to 6 per cent of alcohol.

**Spirits.** Spirits differ from either wines or beers insofar as the latter are not distilled; they therefore also contain nonvolatile organic and inorganic substances, such as salts, etc., not found in the spirits, which are distilled liquids containing only volatile compounds. Moreover, the quantity of alcohol in spirits is very much larger and varies from 45 to 55 per cent. Many distilled spirits may be mentioned: *rye whisky*, made from rye and corn; *Irish whisky*, from barley malt; *Scotch whisky*, from barley; and *bourbon whisky*, made from a mash of grain with not less than 51 per cent corn; *brandy* or *cognac*, by distilling French wines; *rum*, by fermenting and distilling molasses; *gin*, from various grains flavored with juniper berries.

There are various ideas among the laity with regard to the potency and effects of different alcoholic beverages. Mixing drinks is generally believed to produce intoxication more rapidly than drinks of one kind containing the same amount of alcohol. The pharmacologic evidence for this is unconvincing. Drinks produce intoxication in proportion to their alcoholic content if absorption is constant. Little is known regarding the synergistic or antagonistic effects of the minor constituents in alcoholic beverages upon the primary pharmacologic effect of the alcohol.

### SUMMARY OF ALCOHOL IN THERAPEUTICS

1. Alcohol is a peripheral vasodilating agent and is often used for the purpose of dilating the peripheral vessels in the various facets of peripheral vascular disease. It appears that the coronary arteries do not share in this effect elicited by alcohol, unless ingested in excessive quantities.

2. Alcohol is useful in skin massage and serves as a medium for the solution of local antiseptics. It is a detergent.

3. Alcohol is useful in producing nerve degeneration in certain cases of intractable pain (trigeminal neuralgia).

4. Alcoholic beverages serve as *reflex* stimulants for the medullary centers in cases of collapse.

5. Alcoholic beverages (in moderate amounts) stimulate the flow of gastric juice, allay anxiety prior to eating, and may improve the appetite and digestion.

6. Some feel that in the aged moderate amounts of alcohol are a useful source of energy.

7. Alcohol serves as an excellent solvent for many vegetable drugs. It is also a dependable preservative.

8. Alcohol elicits a definitive analgesic action and is used occasionally by intravenous injection (10 to 20 per cent solution) to produce postoperative analgesia.

### SUMMARY OF THE PATHOLOGIC RESPONSES TO ALCOHOL

Formerly, alcohol was thought to cause definitive heart disorders, kidney damage, and various other organ pathology. There has been little scientific evidence to substantiate these views. Clinical observations indicate that alcohol is a factor in cirrhosis of the liver. A history of chronic alcoholism is present in about 50 per cent of the cases. Vitamin deficiency and imprudent dietary habits are likely to be contributing factors.

In addition to the symptoms resulting from an acute drinking bout, such as thick-coated tongue, bloodshot eyes, and a gastritis of varying degrees (all of which are temporary), most of the pathologic findings, as such, are found in disorders in the neuropsychiatric field. This includes encephalopathies of various types, neuropathies, and behavior disturbances (psychopathology), as evidenced by personality, emotional, or mental deviations from the individual's usual behavior or from that commonly accepted as usual by society.

The following are syndromes in which alcohol plays a very important part in producing the clinical picture. (In most cases these are associated with vitamin deficiencies because of inadequate food intake while drinking.)

1. Acute intoxication with excitement
2. Acute intoxication with stupor
3. Acute intoxication with convulsions
4. Delirium tremens
5. Acute and chronic hallucinosis
6. Mental deterioration and dilapidation
7. Korsakoff's psychosis
8. Personality and ethical deteriorations
9. Chronic depressive reactions
10. Paranoid developments

### OTHER ALCOHOLS

The generic term alcohol includes many substances which are important from a pharmacologic standpoint. Some are solvents, some are industrial chemicals, and others enter into foodstuffs. As they contact the living organism, our attention is accordingly drawn to them.

### Methyl alcohol ($CH_3OH$).

Methyl alcohol (methanol) was formerly called "wood alcohol" because it was prepared by the destructive distillation of wood. It is prepared catalytically today from carbon monoxide and hydrogen.

It is a clear mobile liquid without color. It boils at 64.7°C. Methyl alcohol is an excellent solvent for shellac, volatile oils, and resins. It is also used in ethyl alcohol as a *denaturant*, *i.e.*, to render the latter unfit for beverage purposes and thus avoid the excise tax on beverage alcohol.

Alcohol is rapidly oxidized in the body to carbon dioxide and water. Methyl alcohol is slowly oxidized, forming the toxic products formaldehyde and formic acid. It is of interest that methanol has been found in the blood and expired air of normal subjects. Western and Osburn (1949) found 0.025 to 0.245 mg./l. of methanol in blood. Eriksen and Kulkarni (1963) found 0.06 to 0.45 (av. 0.24) mg./l. of methanol in expired air. These analyses were made by gas chromatography, and each of the 9 subjects showed the presence of methanol in his breath. The presence of even small amounts of methanol in expired air is indicative of its presence in the tissues in minute quantities.

Methyl alcohol is readily absorbed from the gastrointestinal tract. It is also partially absorbed through the skin and absorbed rapidly by the lungs. As little as 2 parts of methanol per 1000 parts of inhaled air will cause definite tissue damage if breathed over a period of time.

Methanol is distributed in the various tissues of the body proportional to their water content. The lowest concentrations are found in the bone marrow and fat; the highest concentrations are found in the liver, kidneys, and gastrointestinal tract. In the oxidation of methanol to formaldehyde and formic acid, the liver plays the principal role. The oxidation of formaldehyde to formate is very rapid. After the ingestion of methanol little formaldehyde can be identified in the tissues; however, formate is present in relatively large quantities.

Smith (1961) showed that the liver catalase inhibitor 3-amino-1,2,4-triazole did not affect ethanol oxidation in the rat, but methanol oxidation was reduced 50 per cent. Xanthine doubled the rate of oxidation of methanol oxidation *in vitro* but did not influence the oxidation of ethanol. Ethanol appears to be oxidized by alcohol dehydrogenase and methanol by catalase. In equimolar quantities ethanol inhibits the oxidation of methanol. Smith suggests that ethanol probably inhibits methanol oxidation in the liver by competing for the active site on the enzyme catalase, although ethanol is not oxidized by this enzyme.

Like ethanol, methanol is a depressant to the central nervous system. The symptoms of methanol intoxication in man have little in common with the syndrome of inebriety produced by ethanol. Its intoxicating effect is slight and is usually masked by the simultaneous ingestion of large quantities of ethanol. The acute toxicity of methanol in laboratory animals is less than that of ethanol (Hunt, 1902). This, however, does not prevail in man, since 1000 mg./kg. of methanol may produce blindness and death (Röe, 1955).

The symptoms of methanol poisoning in man are often delayed for several hours. *Weakness*, *anorexia*, *nausea*, and *headache* appear first. These are followed by *vomiting*, *dyspnea of Kussmaul's type*, *severe tenesmus*, and *pains in the back and legs*. *Abdominal pain* is usually excruciating. *Ocular symptoms* follow, first *amblyopia* and then *amaurosis*. *Stupor* and *coma* prevail, with *failure of respiration*. The alkali reserve of the blood is depleted (Röe, 1955).

The action of methanol on the ganglionic retinal cells is specific and often irreversible. The effects are most prominent in the cell nuclei, which often appear to protrude beyond the wall of the cell. Röe (1955) emphasizes that the retinal damage observed in man does not occur when methanol is administered to many laboratory animals. Cooper and Marchesi (1959) demonstrated the competitive inhibition of hexokinase by formaldehyde. Their experiments suggest that small amounts of formaldehyde inhibit retinal hexokinase and, if continued for a sufficiently long time, may result in retinal degeneration and blindness. Rabbits whose eyes were injected with small levels of formaldehyde showed blurred pigment streaks. Other rabbits that were treated with formaldehyde and glucose to protect the hexokinase showed no changes after a 12-day period of observation. This is an interesting contribution to our knowledge of methanol-induced blindness.

Röe's hypothesis regarding methanol intoxication seems plausible. He postulates that methanol or one of its metabolites inhibits cellular oxidation in man. Lactic, formic, and other organic acids accumulate in the tissues, producing acidosis, which further diminishes oxidative activity. The administration of alkali reverses the process. The possibility of formate uniting with the iron-bearing cytochrome enzyme is also worthy of consideration, as formic acid unites readily with ferrous and ferric iron. In proportion to its iron content the retina has a greater oxygen consumption than other tissues. This may be a factor concerned with the retinal damage of methanol poisoning.

Cooper and Kini (1962) showed that formaldehyde was a potent agent in uncoupling oxidative phosphorylation on the mitochondria of retinal cells.

The treatment of methanol poisoning centers around the combating of the severe acidosis. Sodium bicarbonate and glucose are given intravenously. Bicarbonate may also be given orally. The bicarbonate must be adequate, amounting to 100 gm. or more in 12 hours. Subsequent doses are determined by plasma $CO_2$-combining power tests. Artificial respiration in an atmosphere of oxygen is desirable. Relapse into acidosis should be carefully avoided. Röe (1955) contends that since ethanol preferentially competes with methanol for enzymic oxidation, ethanol given in small quantities guards against relapse. Gilger *et al.* (1959) studied the effects of the ocular protection of ethanol in methanol poisoning in monkeys. In 4 of 5 monkeys treated with ethanol after the ingestion of methanol, no eye changes were observed. In all of the ethanol-treated monkeys the metabolic acidosis evoked by methanol was either retarded or reversed. They recommend the administration of 0.75 gm./kg. of ethanol followed by 0.5 gm./kg. every 4 hours for about 3 days in methanol poisoning. It is clear that the sooner the ethanol treatment is instituted after the ingestion of methanol, the more effective will be the inhibition of methanol oxidation.

Bed rest is essential. Chew (1946) recommends keeping the patient's eyes covered until visual disturbances have disappeared. He also found nikethamide a useful drug to combat the respiratory depression.

### The higher molecular weight alcohols.

The alcohols of the aliphatic series of hydrocarbons present an interesting study in relationship of chemical constitution and pharmacologic response. This series has been the subject of numerous toxicologic studies, using the whole gamut of laboratory animals. In general it appears that narcotic activity varies directly as molecular weight increases. As the molecular weight of the homolog in the series increases, the oil/water coefficient increases also and hence the latter physical property parallels narcotic activity in most cases.

The activity against bacteria increases in general with molecular weight to octyl alcohol. The secondary alcohols are less active than the normal alcohols, and the corresponding tertiary alcohols are less active than the secondary. Similar data confirm these findings with *E. coli* and *Staphylococcus aureus* (Kokko, 1939).

### The polyhydric alcohols.

Chemically the polyhydric alcohols are those which contain 2 or more hydroxyl groups attached to a hydrocarbon radical. The simplest of these compounds is *ethylene glycol*, $C_2H_4(OH)_2$. It is hydroxy ethanol. Many other glycols have come into prominence in recent years. They are industrial solvents and antifreeze mixtures. Some of them are available as solvents for drugs, such as *propylene glycol* ($CH_3 \cdot CH \cdot OH \cdot CH_2 \cdot OH$).

Great caution should be exercised in the use of new solvents for drugs or foods. Long-term toxicity studies are necessary. Much harm has been done by the use of diethylene glycol as a solvent for sulfanilamide. The acute toxicity of these compounds, which may be low, is no faithful criterion of what chronic toxicity the substance might evoke.

The polyhydric alcohols do not exhibit the strong narcotic effect on the central nervous system that is elicited by the monohydric alcohols. Propylene glycol is capable of serving as a precursor of glycogen in the liver of the rat. Glycerin behaves in the same manner. When more hydroxyl groups are present in the molecule, as in the sugar alcohols, water solubility is enhanced, hence the oil/water coefficient is diminished, and narcotic activity is correspondingly less. When fed to man in reasonable quantities these substances do not behave like their analog with one hydroxyl group in the molecule, namely, hexyl alcohol. The latter is a strong narcotic, whereas the sugar alcohols, the hexahydroxy hexanes, may serve as foods. Because of the recent interest in the sugar alcohols as dietary adjuncts, consideration of their metabolic fate and pharmacologic action is given.

### The sugar alcohols.

Owing to the close chemical relationship existing between the sugar alcohols and other carbohydrates and the conversion of the former into glycogen in the animal, the fate of the sugar alcohols in the animal body is of signal importance. In addition, the occurrence of the sugar alcohols in many edible plants warrants the study of their metabolic patterns. Besides, in recent years the synthesis of such members of this class as sorbitol and mannitol as inexpensive commercial chemicals has opened new areas of application and usefulness for these substances. This applies not only to the sugar alcohols but also to a multiplicity of their derivatives which are appearing in ever-increasing abundance as solvents and as emulsifying and dispersing agents for foods and vitamins.

The sugar alcohols or carbohydrate alcohols may be classified as a group of compounds obtained as reduction products of ketoses or aldoses or homologous compounds. Further, they may be considered as compounds of carbon, hydrogen, and oxygen, containing typically one hydroxyl group for each carbon atom present in the molecule. Such a classification in the aliphatic series of hydrocarbons begins with methyl alcohol and ascends in the series through ethylene glycol and glycerol to mannoheptitol and higher alcohols. The names *saccharols*, *glycitols*, and *polyols* may be assigned to the class of compounds.

Substances such as methyl alcohol and ethylene glycol are studied under categories other than the sugar alcohols. Furthermore, in common parlance, the term *sugar alcohol* as a rule refers to the hexahydric alcohols, and their availability as food in the human diet warrants special study of their pharmacologic actions and metabolic patterns.

**Glycerin** $C_3H_5(OH)_3$. The occurrence of glycerol (glycerin) as a normal constituent of edible fats and its close chemical relationship to glyceric aldehyde, an intermediate metabolite of glucose, have made it the subject of exhaustive metabolic study. *In vitro*, glycerol is oxidized to dihydroxy acetone by hydrogen peroxide. It is also oxidized by the *Acetobacter suboxydans* to dihydroxyacetone *in vitro*. When administered to phlorhizinized dogs, glycerol is excreted in the urine as extra glucose. Likewise, it was demonstrated that diabetics excreted additional sugar when glycerol was ingested.

Glycerol is an effective and efficient precursor of glycogen when administered to the rat by stomach tube. It has been shown that the content of glycogen in the liver rose from a fasting value of approximately 0.15 per cent to 3 per cent. In fact glycogen formation from glycerol in the white rat is comparable to that obtained from the feeding of an equivalent amount of glucose.

Glycerin solutions are *demulcent* to mucous membranes. It is an excellent solvent for vegetable extractive material such as tannins. In its concentrated form it is hygroscopic and hence dehydrating to tissues. Large quantities of 20 to 30 ml., ingested orally, produce a burning sensation and a sweetish taste in the mouth. Its action, which is a local action in the gastrointestinal tract, is laxative in character.

**Mannitol** is a typical hexahydric alcohol which has the composition $C_6H_8(OH)_6$.

D-Mannitol, mannite, or manna sugar, is the name applied to this hexahydric alcohol, which is widely distributed through the vegetable kingdom. It comprises as much as 75 per cent of the sweet medicinal exudation known as manna, *Fraxinus ornus*. For years manna has been used as a mild laxative. The compound was isolated first by Proust in 1806. The early metabolic studies on mannitol were carried out with the naturally-occurring alcohol in manna, which is D-mannitol.

Carr *et al.* (1933), using mannitol obtained from natural sources, showed that it was capable of serving as a precursor of glycogen in the liver of the white rat.

From this and other investigations (Carr and Krantz, 1945), it seems that the fate of mannitol in the animal body proceeds according to the following pattern—absorption from the alimentary tract, partial conversion to glycogen in the liver, and the elimination of much of the sugar alcohol unchanged in the urine.

Upon intravenous injection mannitol is filtered by the glomeruli and not appreciably reabsorbed by the tubules. It may be used for the measurement of the glomerular filtration rate. Clinically mannitol is used in 2.5 per cent solutions as an irrigating fluid in transurethral resection of the prostate. It appears to be superior to water for this purpose because it is nonhemolytic.

Mannitol is also available in 25 per cent aqueous solution for intravenous use in the treatment of cerebral edema and hypoxia. Its value depends upon its action as an osmotic pressure diuretic. Urea solutions are used for the same purpose. Shaw *et al.* (1962) compared mannitol with urea in the treatment of cerebral hypoxia in dogs. Mannitol appeared to possess advantages over urea in that surviving animals treated with mannitol displayed no neurologic damage, in contrast to the urea-treated animals.

**Sorbitol** is the most generally used of all of the hexahydric alcohols. Sorbitol is a white, crystalline solid which elicits a cooling, sweet taste. It is mildly laxative. Usually 30 to 50 gm. are required to produce purging.

The cost of sorbitol obtained from natural sources considerably limited its early metabolic studies in this country. However, European investigators have carried on rather extensive clinical studies with sorbitol during the last 20 years. European methods of producing sorbitol in commercial quantities seem to antedate ours by several years. Sorbitol was introduced into therapeutics in Europe under the name of "Sionin" by Thannhauser and Meyer (1929).

When sorbitol became available commercially in this country, many laboratory workers set forth unequivocal evidence to show that in the rabbit, mouse, and rat, the compound was a precursor of glycogen. Ellis and Krantz (1941) confirmed this observation with respect to the liver of the *Macaca rhesus* monkey.

Because sorbitol has possibilities in normal and diabetic individuals as a substitute for other carbohydrates, chronic feeding studies were conducted by Ellis and Krantz (1941) in *Macaca rhesus* monkeys and man. Later Ellis and coworkers (1943) extended these studies through 3 successive generations of white rats. It was observed that the feeding of 3 gm. of sorbitol a day to monkeys over a period of 3 months produced no histopathologic findings in the viscera nor gross toxicologic symptoms. In man, the ingestion of 10 gm. of sorbitol daily over a period of one month produced no significant changes in the nonprotein nitrogen, carbon dioxide-combining power of the blood, or red blood cell count. The phenolsulfonphthalein test indicated no functional kidney impairment. In the white rat, diets consisting of 5 per cent sorbitol did not affect deleteriously the rate of growth, liver-glycogen storing capacity, or important metabolic viscera of the rat through 3 successive generations. The use of sorbitol in diabetes is discussed on page 872.

### POLYSORBATE 80

A series of compounds resulting from the reaction of sorbitol and mannitol esters with a varying number of moles of ethylene oxide has been made available commercially as Tweens. These compounds serve as dispersing agents. They are employed as dispersing agents for volatile oils, oil-soluble vitamins, and many other edible and drug products.

**Polysorbate 80, U.S.P. (polyoxyethylene sorbitan monooleate, "Tween 80").** Polysorbate 80 is a complex mixture of polyoxyethylene ethers of mixed partial oleic acid esters of sorbitol anhydrides. It is a lemon to amber colored, oily liquid which is very soluble in water. Polysorbate 80 is used as a dispersing agent for many oil-soluble foods and drugs. The pharmacologic responses of polysorbate 80 were studied by Krantz *et al.* (1951 *et seq.*). Its availability as a dietary adjunct in man was shown. Jones (1948) demonstrated that the oral ingestion of polysorbate 80 promoted the absorption of fat and vitamin A from the alimentary tract in patients with steatorrheas of various etiologies.

Polysorbate 80 has been found especially useful in promoting the absorption of fat from the alimentary tract in *sprue*, *celiac disease*, *postoperative conditions which short-circuit portions of the small intestine*, and *pancreatic fibrosis*. Jones and Culver (1948) recommend 6 gm. daily as a minimal dosage schedule. This amount should be given with the meals in 3 doses. Larger daily quantities up to 15 gm. may be desirable in severe steatorrhea. The substance may be administered in 0.5-gm. capsules or mixed with tomato or orange juice.

Long-continued use of polysorbate 80 is apparently without harmful effects. The substance is split by pancreatic and blood lipases. The oleic acid portion of the molecule follows the usual metabolic pattern for this edible fatty acid. Only 5 per cent of the polyoxyethylene sorbitan fraction of the molecule is absorbed and excreted by the kidneys unchanged; the remainder is excreted in the feces.

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# 22

# *Central Nervous System Depressants. The General Anesthetics*

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## General Aspects

General anesthetic agents are substances used to abolish the perception of stimuli, produce a hiatus in consciousness, and obliterate motor activity. Ether and chloroform are typical anesthetic agents. No class of substances has contributed more to human welfare than the anesthetics. They have made modern surgery possible and have changed the operating room from a chamber of horrors to a place where the tranquility of unconsciousness supervenes.

Pain is one of the arch enemies of man. From the dawn of history he has sought a surcease from pain. Opium, mandragora, and alcohol have been used to obtund the pain of surgery. Modern anesthetic agents have been used for a little over a century. The discovery and the introduction of the volatile anesthetic agents into medicine is one of the most dramatic and fascinating stories of medical history.

### Historical Summary of the Discovery of the Volatile Anesthetics

**Nitrous oxide.** In 1772 Joseph Priestley the discoverer of oxygen, made nitrous oxide or "laughing gas." Priestley was not aware of its capacity to affect the central nervous system and produce anesthesia. In the year 1800 Sir Humphrey Davy remade Priestley's gas and in a letter to one of his friends Davy wrote as follows: "I remade this gas that Joseph Priestley discovered, inhaled it, and my pulse jumped 20 strokes. I danced around my laboratory like a mad man." He suggested to the medical profession that in all probability this substance might be useful in the alleviation of pain produced by surgery. But a skeptical profession ignored the suggestion. Davy persisted. He was called on by Count Rumford, the founder of the Royal Institution of London, the Prime Minister, and Mr. Wedgwood, who were all anesthetized with laughing gas. Yet they did not conceive of its application to surgery.

The scene shifts across the Atlantic from England to this country. Four decades have passed The year is 1844. The exact date is December 10, and in Hartford, Connecticut, a ripple of enthusiasm stirs the town. A miracle worker is coming to town. He is Gardner Q. Colton, lecturer on chemical phenomena. He has a new gas, and this gas is reputed to make people act beside themselves. It can make a very peaceable man pugnacious. It can throw him into fits of anger. That afternoon a dentist, Horace Wells of Hartford, Connecticut,

had flash through his scintillating intellect the idea of the possibility of using this gas in dentistry. That evening he took Mrs. Wells to hear Dr. Colton. Reluctantly she went. They occupied positions up in the front row. It was advertised that the front row would be occupied by strong men so that if any of these people who were put under the influence of laughing gas would tend to work harm on the audience, the 9 men on the front row would take care of them.

The performance started. A young man, clerk in a drugstore, whose name was Cooley, was called to the stage and then the black silk bag was squeezed, and Gardner Colton allowed Mr. Cooley to inhale Priestley's gas. Cooley became greatly exhilarated. He jumped off the platform, darted down through the audience, hit his shin a dreadful blow against one of the oaken benches, ran madly through the auditorium, and then slumped down. Horace Wells followed him closely. He looked at his legs. He saw an ugly bruise and blood exuding. He inquired, "Cooley, did you feel pain?" Cooley replied, "I didn't know it happened." Wells cogitated upon the experience of that evening.

The next day he communicated with Dr. Colton and with a friend, Dr. Riggs, and Mr. Cooley. They went to his dental office, and there Dr. Riggs extracted one of the teeth of Horace Wells while Wells squeezed Dr. Colton's bag. Wells did not whimper. The era of painless dentistry had been established, and man had acquired a surcease of pain.

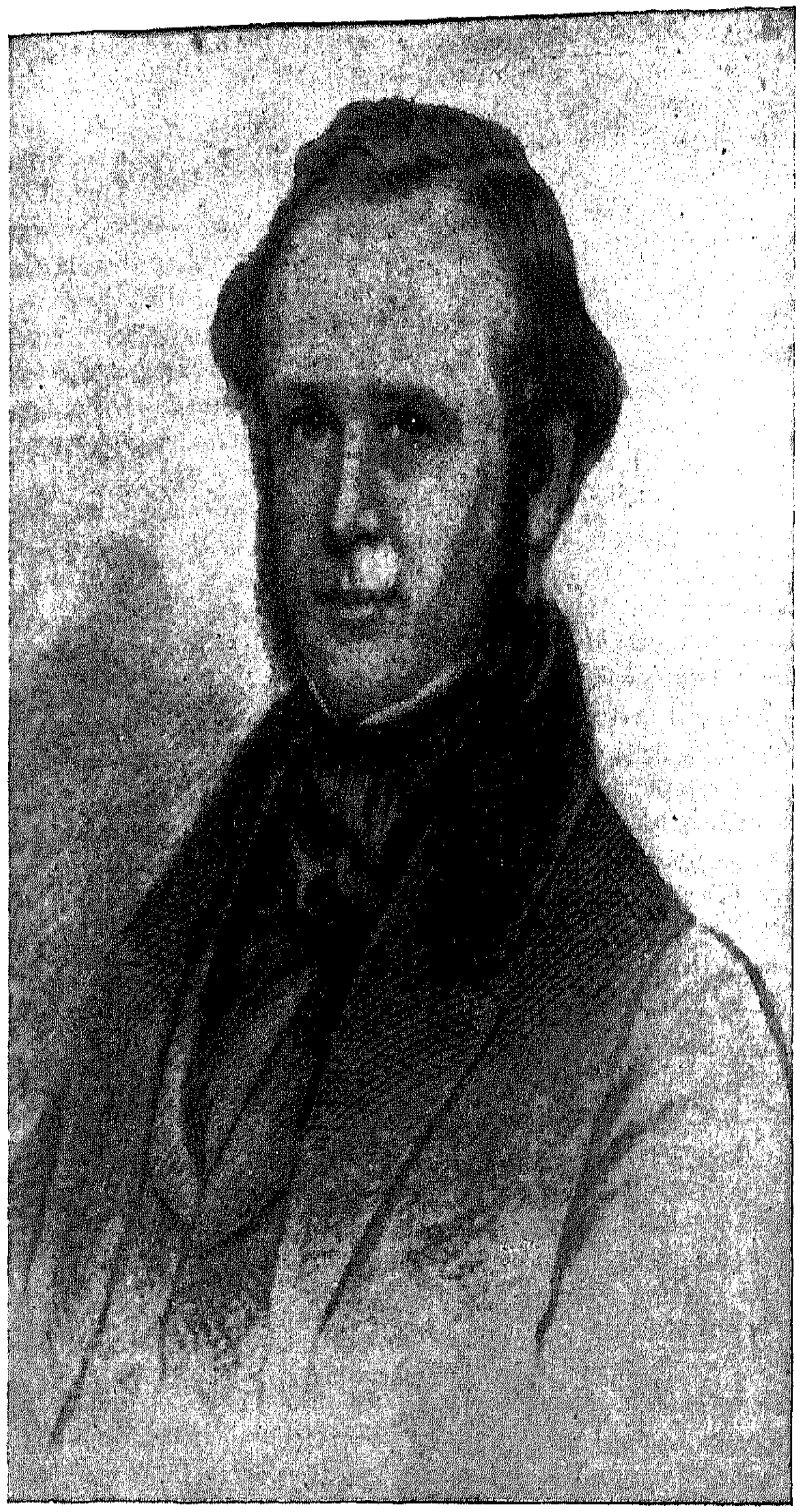
Wells did not succeed in getting the use of nitrous oxide well established in his native town of Hartford. Owing to ill health he gave up his dental practice. He was then associated with Dr. William T. G. Morton. Wells went into the business of giving entertainments on natural phenomena and making shower baths in order to recuperate his health. However, he could not get from his mind this fundamental concept that *when man is in anger, in passion, in rage, or in a period of exuberance or exultation, he does not feel pain. Further, if by a chemical agent such as nitrous oxide one can produce similar psychic states, one could relieve pain*. And that was the fundamental idea underlying anesthesia. It was the centerpiece, and everything else was embroidery around it.

Wells had quite abandoned his researches in the field of general anesthesia when a letter came to him from Dr. Morton, who had gone to Boston to attempt to patent a liquid by the name of "ether" which he was using in the alleviation of pain. Wells became interested. He traveled rapidly to Boston. There he tried to apply nitrous oxide again in the extraction of a tooth from a student at Harvard University. The student cried out, "I felt the pain!", and they hissed Wells out of the room as a charlatan. The difficulty with Wells at that time was that he had not mastered the technic of regulating the dose of nitrous oxide.

In 1848 Wells set up a dental practice in the City of New York, under the slogan of "painless dentistry, extraction of teeth without pain." Early in that new practice in New York he began to experiment on himself, using chloroform this time to alleviate pain. Later he took his own life by severing one of his femoral arteries while inhaling chloroform presumably to obtund the pain. Wells died never realizing what a great boon he had given to all humanity.

**Ether.** As Wells passed, his spirit marched on through the decades. In Georgia, Crawford W. Long, a physician, in 1841 heard of a liquid that was being used to cause people great exhilaration comparable to alcoholic inebriety, and the young physician became interested. He invited many people into his home, and he used ether for inhalation purposes. These people would become exhilarated—ether frolics were born, and they became very popular. It happened one day a colored boy looking in the window was snatched in and given a great amount of ether. He went deep down into surgical anesthesia, and they were very much afraid they would be unable to awaken him. When he came to, through the mind of Crawford W. Long flashed the possibility of using ether as an agent to relieve pain. The people in Georgia, particularly the medical profession, were skeptical about these ether frolics. Crawford W. Long was warned by the people to stop using this substance. He was dissuaded from going on with his experiments even though he had used ether to remove a cyst from the neck of Mr. James Venable, and Mr. Venable apparently felt no pain.

From the South the scene of general anesthesia pushed north, and went from the hands of a physician again into the hands of a dentist as we look into the work of Dr. Morton, associate of Dr. Wells. In Boston, Morton had come in contact with a chemist named Jackson. Jackson had anesthetized himself many times with diethyl ether, and he informed Morton that ether was not particularly harmful, that one could take it—could inhale it, go under narcosis, and awaken again apparently with impunity. And so Morton saw the possibility of using this substance in surgery. In Boston, he persuaded the surgeon, Dr. John C. Warren, a descendant of the famous Dr. Warren associated with General Putnam of the Battle of Bunker Hill, to permit him to use ether on one of his patients. The year was 1846. The date was October 16, and the group in the operating room that morning was skeptical. Morton was busy at the shop of Mr. Chamberlin who was making the mask for him. Chamberlin had promised to have



HORACE WELLS

1815–1848

*The discoverer of the use of nitrous oxide as an anesthetic*

"I was led to believe that the inhaling of any exhilarating gas, sufficient to cause great nervous excitement, would so paralyze the system as to render it insensible to pain." (*From "Triumph Over Pain" by Rene Fülöp-Miller, copyright 1938. Used by special permission of the publishers, The Bobbs-Merrill Company.*)

the mask ready at 9:30, and it was already 10:00 o'clock. In the operating room there were sneers, and someone declared, "Another miracle worker whose miracle will not work out." Even Dr. Warren wondered if Dr. Morton would appear. Breathlessly he entered the operating room as the group in the balcony in their long frocktail coats waited to see what would happen. Then carefully with his new mask Morton began to drop diethyl ether slowly, slowly, and then came the memorable statement—that has echoed down through the decades, when Dr. Morton looked up and said to Dr. Warren, "Dr. Warren, your patient is now ready." Dr. Warren looked down at the table and

turning to the skeptics in the audience said, "Gentlemen, this is no humbug. Mr. Abbott is fast asleep."

**Chloroform.** In England scientists began to look for substances as good as or better than diethyl ether. They knew of the experiences of Henry Hickman, who preceded Wells, and many other people in this country performing anesthetic experiments on animals. We look in on the Professor of Midwifery in the University of Edinburgh, James Y. Simpson. Simpson had tried many different compounds. They did not work. They were not so good as ether or they were poisonous, so he discarded them. One day as he was fumbling through the papers on his desk he came across a vial of colorless, volatile liquid first made by the German apothecary Justus von Liebig. He thought, "Oh, I have tried everything else, I might just as well try this chloroform." So he anesthetized himself to unconsciousness, and later his associates Keith and Duncan, apparently with impunity.

After many trials in obstetrics and in surgery, chloroform found its place along side of nitrous oxide and ether as a general anesthetic.

Records which appear to be authentic indicate that chloroform was discovered by Dr. Samuel Guthrie of Sackets Harbor, Jefferson County, New York, 17 years prior to its use by Simpson. Guthrie was also familiar with some of its interesting pharmacologic properties.

**Ethylene.** There were 7 barren decades in the field of general anesthesia. In the year 1922 Arno B. Luckhardt of the University of Chicago became acquainted with the observation of Crocker and Knight that carnations stored in certain places withered rapidly. He wondered about carnations. An analysis of the air showed there were traces of ethylene in the air. That was the cause of the carnations withering. If this ethylene so affects plant protoplasm, what effect does it have upon animal protoplasm? So Luckhardt tested ethylene on frogs, on cats, on dogs, on monkeys, and ultimately anesthetized himself several times to unconsciousness. In 1922 ethylene was added to the list of general anesthetics.

**Divinyl oxide.** In 1930 it occurred to Chauncey Leake, then at the University of California, that it might be a prudent idea to combine ethylene, which is characterized by such a smooth induction, with ethyl ether, which is characterized by excellent abdominal relaxation. He considered that a hybrid molecule might have advantages, and so the compound was prepared, *divinyl oxide—Vinethene.* Vinethene is useful in dental practice owing to the rapidity of induction. Its potency is about four times that of diethyl ether, and it is recommended for operations of short duration.

**Cyclopropane.** In 1929 at the University of Toronto, Lucas and Henderson, while looking for an agent better than ethylene, used cyclopropane as a general anesthetic. This anesthetic gas gives deep surgical anesthesia in concentrations of 15 per cent compared with 90 per cent with nitrous oxide or 80 to 90 per cent of ethylene.

**Newer anesthetics.** During the last 2 decades, the authors have studied numerous compounds pharmacologically for their suitability as volatile anesthetic agents. Two of these are available clinically—Vinamar (ethyl vinyl ether) and Fluoromar (trifluoroethyl vinyl ether). The latter compound was the first fluorinated ether used clinically. It was the forerunner of halothane and methoxyflurane. These newer agents are potent anesthetics and have the advantage of exhibiting no fire or explosive hazard.

**Properties of the ideal anesthetic agent.** Since the introduction of ethyl ether and chloroform as inhalation agents, an avalanche of new compounds has followed. The ideal anesthetic agent has not yet been found. All existing agents have some drawbacks. The ideal anesthetic agent should:

1. Produce rapid and smooth induction
2. Be nonirritating to mucous membranes
3. Be potent
4. Be nonflammable
5. Be stable to soda lime, light, and heat
6. Not sensitize the myocardium to epinephrine
7. Not produce severe hypotension
8. Be nontoxic to brain, liver, heart, and kidney tissues
9. Not produce nausea or vomiting
10. Produce not only anesthesia but also analgesia and muscle relaxation
11. Be compatible with ancillary drugs used in anesthesia
12. Be inert (essentially nonmetabolized)
13. Be economical and useable with existing anesthetic equipment.

In summary, an anesthetic should provide:

1. A safe and pleasant anesthesia for the patient
2. Sufficient relaxation so that surgery can be readily achieved
3. Prompt recovery of the patient to preoperative physiologic norm.

Even though we do not have the ideal anesthetic agent, with the combinations of anesthetics and ancillary drugs now available, it does appear

TABLE 22-1

*The Standard Sequence of the Depression of the Brain by Blood Borne Anesthetics*

(Harris, 1951)

| Standard Sequence of Biological Response | Guedel's Classification (1937) |
|---|---|
| Depression of the higher centers | Stage 1<br>Analgesia |
| Amnesia | Stage 2 |
| Cooperative stupor | Delirium |
| Noncooperative stupor | Stage 3 |
| Anesthetic sleep | Surgical anesthesia |
| Depression of areas of sensory coordination | Plane 1, sleep<br>Plane 2, sensory loss |
| Loss of the ability to react to external stimulus | Plane 3, loss of muscle tone<br>Plane 4, intercostal paralysis |
| Depression of areas of motor coordination | Stage 4 |
| Loss of muscle tone in | Medullary paralysis |
| Small muscle groups | |
| Large muscle groups | |
| Intercostal muscles | |
| Depression of the vital medullary centers | |
| Failure of the respiratory center | |
| Failure of the vasomotor center | |
| Failure of the cardiac center | |

that in skilled hands these objectives can be achieved.

**Stages and physical signs of anesthetic depth.** In a general way the action of volatile anesthetics may be divided into 4 stages. These are (1) preanesthesia, the induction stage; (2) delirium or dream stage; (3) surgical anesthesia, the operative stage; and (4) the stage of medullary paralysis. The anesthesiologist has further divided the stages of anesthesia and subdivided the surgical stage into various anesthetic planes. Certain physical signs accompany the changes in depth of anesthesia. These are set forth in table 22-1 along with a modified Guedel classification of the stages of anesthesia. The character and duration of each stage are dependent upon the anesthetic agent employed.

These classical stages of anesthesia are readily discernible when a comparatively weak anesthetic like ether is administered to a patient without adequate premedication or the use of a rapid-inducing agent. However, this seldom occurs. Adequate premedication, the use of rapidly-acting induction agents, and the general use of more potent anesthetics such as halothane enable anesthesia to be achieved so rapidly that the preliminary stages are not readily recognized.

### ABSORPTION, DISTRIBUTION, AND EXCRETION OF VOLATILE ANESTHETICS

The most important factors influencing the uptake, distribution, and elimination of anesthetics are (1) *The concentration of the drug in the inhaled mixture* is expressed in volumes per cent, or its partial pressure in millimeters of mercury. A high partial pressure establishes a steep gradient from the lungs to the blood promoting rapid saturation; when the drug is discontinued, the pressure gradient is reversed favoring the elimination of the anesthetic via the lungs. (2) *The tidal volume* directly affects the dose of anesthetic inhaled per unit time. Shallow breathing causes slow diffusion and prolonged induction; deep breathing increases the amount of drug in the alveolar air, thus hastening induction. (3) *The functional residual capacity* is the air space in the lungs in contact with the alveolar surface. The total volume is large in emphysema; thus, diffusion occurs slowly delaying saturation and desaturation of the blood. In children this volume is small, and sudden deep inspirations cause rapid diffusion and deepening of anesthesia. (4) *The solubility of the drug in the blood* is directly proportional to its partial pressure and also dependent on its solubility coefficient (air-blood ratio) at body temperature. (5) *The solubility of the anesthetic* in the tissues is dependent on the tissue-blood coefficient of the drug, *i.e.*, the manner in which the agent is distributed between these 2 phases. (6) *The permeability of the alveolar membrane* is only of special concern in cases of edema, fibrosis, and increased secretions which interfere with the absorption of gases by decreasing the alveolar surface. (7) *The blood flow through the lung capillaries* becomes important only when the blood volume is markedly reduced, when capillaries are not patent, or when circulation time is significantly altered. (8) *The blood supply to the different body tissues* controls the amount of drug to which the tissue is exposed. The tissue-blood partition coefficient is different for each agent and determines the manner of drug distribution between these 2

phases. Tissues with abundant blood supply are more readily equilibrated with the agent dissolved in the blood.

**Metabolism.** The volatile anesthetics produce their effect irrespective of the manner of administration provided they reach the central nervous system. The standard mode of administering these agents is by inhalation. The volatile anesthetics enter the body, produce anesthesia, and leave the body essentially unchanged. However, it has been shown that ethyl ether, halothane, chloroform, and methoxyflurane are biotransformed in amounts of 1 to 5 per cent as demonstrated by $C^{14}O_2$ in the respired air of rats receiving labeled anesthetics (Butler, 1961; Van Dyke, 1963).

**Absorption.** When the anesthesiologist places the mask over the nostrils and mouth of the patient, the foregoing principles and factors are involved as follows.

1. The greater the concentration in the inhaled air, the greater will be its partial pressure (Dalton's law). The pressure gradients established between (1) the inhaled concentration and that of the alveoli, (2) the alveoli and the blood and (3) the blood and the tissues will determine the direction of flow of the anesthetic agents.

2. The greater the partial pressure of the agent, the greater will be its solubility in the blood, the liquid into which it passes (Henry's law). That is, the weight of the gas dissolved in a solvent is proportional to its partial pressure. The solubility is also dependent on the temperature. As the temperature increases, the amount of gas dissolved in the blood decreases. This becomes an important concept to consider during hypothermia. The presence of other dissolved substances in a solvent such as increased salt concentration reduces the solubility coefficient of gases in that medium (Markham and Kobe, 1941). Featherstone *et al.* (1961) observed that solutions high in albumin dissolved more anesthetic gas than those low in this protein.

3. The lower the density of the mixture of anesthetic gases, the greater will be its rate of diffusion (Graham's law). Hence, helium-oxygen mixtures with an anesthetic in cases of obstruction of the airway anywhere between the alveoli and the lips have an advantage. Lighter gases diffuse more rapidly in and out of the alveoli and the bronchi. They lessen the effort of ventilation. The diffusion of an anesthetic across a membrane is influenced not only by its density but also by its solubility in the membrane, the pressure gradient, the surface area and the thickness of the membrane.

4. The anesthetic is partitioned between the alveolar air-blood and blood-tissues according to the Law of Distribution. Distribution or partition coefficients can be expressed in different terms; however, the solubility of inert gases in liquids is expressed in one of two ways as follows.

A. It is expressed as an *absolute* quantity of gas in a known quantity of liquid. An example of this is the Bunsen absorption coefficient; defined as the volume of gas which dissolves in a given volume of solvent, when its partial pressure is one atmosphere and the temperature is reduced to 0°C.

B. Or the solubility is expressed as the *ratio* of the distribution of a gas or a vapor in equal volumes of two phases at equilibrium. When one of the two phases is a gas, the partition coefficient is called Ostwald coefficient or lambda ($\lambda$). The Ostwald coefficient is defined as *the ratio of distribution of a gas or vapor in identical volumes of a gaseous and liquid phase equilibrated at a given temperature and one atmosphere.* The Ostwald coefficient for ethyl ether (the air-blood ratio) at 37° C. is 15. This indicates 15 parts of ether will dissolve in 100 ml of blood when 1 part dissolves in 100 ml. of the overlying gaseous phase. With an anesthetic the recovery time parallels the Ostwald coefficient. The Ostwald coefficient is one of the primary determinants influencing the rate of uptake and excretion of anesthetic vapors via the lungs.

**Distribution.** The anesthetic is carried to the tissues containing lipids via the blood. It therefore partitions itself out of the blood according to the Law of Distribution. It passes in the direction of its greater solubility. The volatile anesthetics enjoy a high oil/water coefficient; therefore, much greater concentration occurs in the tissues richest in lipids. However, some tissues high in lipids, such as adipose tissue, are saturated and desaturated very slowly because they have a poor blood supply compared to other body tissues. The relative exposure of any tissue to a blood-borne anesthetic necessarily depends on the relative amount of tissue and the quantity of blood flow to that particular area.

The value for relative exposure of an organ to a general anesthetic is derived by dividing the relative blood flow to an organ by the relative mass of that organ. For example, the brain has a relative blood flow of 5 and a relative mass of 3; therefore, the relative exposure of the brain to the anesthetic is 0.6. On the other hand, the ratio for skeletal muscle is 3:100 or 0.03 (Goth, 1961). The figure for relative exposure of a tissue to an anesthetic is a more meaningful indication of the uptake of general anesthetics from the blood stream than the size of the organ or its blood flow considered alone.

As long as the arterial blood contains an anesthetic gradient with respect to the tissues, the agent passes from the arterial blood into the body tissues faster than it passes from the tissues into the venous blood. Ultimately there is an equilibrium established. The gradient no longer exists, and the anesthetic leaves the tissues via the venous blood at the same rate that it is supplied to the tissues by the arterial blood. This condition is referred to as anesthetic equilibrium. It is seldom experienced in practice. It may be approached when using the closed circuit $CO_2$ absorption technic.

**Excretion.** When the anesthesiologist removes the mask, discontinuing the agent, the following equilibria shifts occur in rapid succession.

1. The partial pressure of the anesthetic in the inhaled air is reduced to zero.
2. Therefore, the arterial blood carries no anesthetic agent.
3. The tissues, therefore, enjoy an anesthetic gradient with respect to the blood, and the anesthetic passes from the tissues into the blood, maintaining always its distribution constant.
4. The Ostwald coefficient of the individual agent determines the rate at which the anesthetic is cleared from the blood into the alveolar air. Ethyl ether has an Ostwald coefficient of 15 and halothane 2.3. From these values Larson *et al.* (1962) calculated the per cent clearance of these anesthetic agents in each passage through the lungs when the ventilation is 4 L. per minute and a lung capillary blood flow 5 L. per minute. They calculated that 5 per cent ethyl ether and 26 per cent halothane were cleared from the blood in each passage through the lungs after the drug was discontinued. This is the main reason for a longer recovery period after ethyl ether than after halothane anesthesia.

The volatile anesthetics are mainly excreted in the exhaled air. Small quantities may also be excreted in the urine, through the skin, into various secretions of glands, into the open body cavity during surgery, and into the lumen of the bowel. The rate of excretion is different for each agent and is dependent on its Ostwald coefficient as previously mentioned. The general pattern of the excretion curves is the same; about half of the agent is excreted in the first 30 to 60 minutes after cessation of the anesthesia. The remainder is eliminated more slowly.

## The Response of the Central Nervous System to General Anesthetics

The agents included in this general discussion of the action of volatile anesthetics are ether, chloroform, nitrous oxide, ethylene, cyclopropane, fluroxene, halothane, and other less common agents. The volatile anesthetics produce a depressant action on the central nervous system. The depressant action is preceded by varying degress of excitation. The action on the central nervous axis is a selective descending depression resulting ultimately in paralysis. Many hydrocarbons and volatile organic liquids produce a direct descending paralysis of the central nevous system. However, those which are available as anesthetics exhibit a specific feature of selectivity in their descending depression of the central nervous system. *The anesthetics depress first the reticular activating system, second the cortical areas, third the spinal centers, and fourth the medullary centers.* It is obvious that if the paralysis did not affect the medullary centers last, the compound would not be suitable as an anesthetic agent.

The work of Magoun and his associates established that the reticular formation was involved in the production of sleep and the transmission of pain impulses. French *et al.* (1953) showed that ether and pentobarbital elicited reversible depressant effects upon the midbrain reticular formation. These studies were extended to most of the commonly-used general anesthetics. They observed that anesthesia caused a depression of the potentials from the midbrain periaqueductal reticular formation. The depression of the potentials was a function of the concentration of the anesthetic administered. The depressive effect was not shared by the neuromuscular blocking agents such as *d*-tubocurarine.

Davis *et al.* (1958) demonstrated that anesthesia with ether, chloroform, divinyl ether, and trichlorethylene depressed the amplitude of the evoked responses affecting the midbrain reticular potentials to a greater degree than the thalamic relay evoked response. Of the agents employed ether was found to be the most potent. It is significant, however, that of the agents studied, ether is the least potent anesthetic. This lends further evidence to the concept that general anesthesia is associated with a reversible depression of the midbrain ascending reticular system.

Davis *et al.* (1961) in a continuation of their earlier work investigated the evoked responses of the midbrain reticular formation and the thalamic nuclei in cats under halothane anesthesia. The depression observed with halothane was qualitatively similar but quantitatively different than that observed with the previous compounds. Halothane depressed both regions, with the thalamic area showing by far the more marked effect. There is no explanation for the fact that halothane, a poor analgesic clinically, depresses the region conventionally linked with transmission and primitive perception of pain (the thalamus) more than the other agents studied.

**Mechanism of action of the volatile anesthetics.** The mechanism of the action of the volatile anesthetics has been the subject of study for many years. Its importance as a biological phenomenon cannot be overestimated. Lillie (1916) stated, "The problem of the general nature of anesthesia is a fact inseparable from the wider problem of the nature and conditions of irritability in general." Besides, many of the keys to the nature of consciousness and perhaps behavior patterns might be elucidated if this problem were completely understood.

At the turn of the century Hans Horst Meyer (1899) and E. Overton (1901) expressed their theory of narcosis in the following postulates:

1. All chemically indifferent substances which are soluble in fats and fat-like bodies must exert a narcotic action on living protoplasm, insofar as they can become distributed in it.
2. The effect must manifest itself first, and most markedly, in those cells in which fatty or lipoid substances predominate in the chemical structure and presumably in which they form essential participants of the cell function; *viz.*, in the nerve cells.
3. The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipoid substances on the one hand, and for the remaining body constituents, *i.e.*, principally water, on the other hand. Their efficiency is therefore dependent upon their partition coefficient which determines their distribution in a mixture of water and lipoid substances.
4. Meyer calculated that the molar concentration of chemically inert substances required to produce narcosis, even though they vary in potency, is a fixed value of 0.06 M/L.

One is inclined to call these time-honored postulates a statement of narcotic distribution in the body rather than a theory of narcosis. However, when viewed with respect to our knowledge of cellular respiration many years ago, they were a definite contribution and have stood the test of time.

Ferguson (1939) pointed out that the significance of data on narcosis is much greater when concentrations of the drugs administered are expressed on a thermodynamic scale rather than in volumes per cent. Thermodynamic activity is a measure of those molecules of a given substance which are not involved in nonspecific interactions with other molecules of the same substance or with solvent molecules; in other words, those molecules which are free to exert a specific biological effect. Ferguson further noted that the various theories of narcosis presented in the past were not independent theories; instead, the physical properties of anesthetics which were measured, such as vapor pressure, solubility, surface tension, oil-water coefficient, adsorbability etc. were actually measures of the tendency of a substance to distribute itself between 2 phases. Further, when equilibrium was established, the chemical potential would be the same in each phase. Brink and Posternak (1948) contend that the work required per mole in the transfer of the anesthetic from the pure liquid to the narcotized cell is the same for all substances which produce equal degrees of narcosis at equal thermodynamic activities. They speculate that anesthetics probably produce their effect in regions of the cell in which their molecules fit much as they fit into their own pure liquid.

Mullins (1954) extended Ferguson's theory of thermodynamic activity to include molecular volume. Mullins stated, "Narcosis by chemically inert molecules appears to take place when a constant fraction of the total volume of some non-aqueous phase in the cell is occupied by narcotic molecules. If the narcotic behaves ideally in this non-aqueous phase, the thermodynamic activity of the narcotic multiplied by its modal volume is a constant, about 1 ml./mole."

Wulf and Featherstone (1957) consider these concepts consistent with their hypothesis, namely, that the increasing potency of clinical anesthetic agents parallels in general their van der Waals' physical constants (correction constants in Boyle's law for non-ideal gases). Based upon these data they explain the anesthetic activity of the inert gas xenon. They point out that its anesthetic potency should be equivalent to that of nitrous oxide and ethylene since their van der Waals' constants are essentially the same. Xenon, nitrous oxide, and ethylene do exhibit about the same degree of anesthetic potencies.

Other investigators have attempted to correlate the physical properties of the anesthetic gases with their biological activity. Miller (1961) proposed the theory of "gas hydrates." The gas hydrates are clathrate compounds of a gas encaged in a distorted ice matrix. Helium, hydrogen, and neon do not exhibit anesthetic properties—they form no gas hydrates. Many anesthetic gases form gas hydrates. Miller found a correlation between the pressure of the anesthetic required for surgical anesthesia and the dissociation pressure of the corresponding gas hydrate at 0°C. Although the hydrates are not formed in the body with the pressure of the anesthetic gas, Miller contends that the anesthetic gas will increase the number of hydrates present in neuronal tissue. This forms a sort of "ice cover" at a membrane or protein surface. The ice cover probably lowers conductance, "stiffens up" the lipid membrane, "plugs up" the pores in the membrane and thus reduces transmission of neuronal impulses at synapses.

Pauling (1961) proposed a challenging hypothesis of anesthetic activity. Most views of anesthetic action have included the affinity of the agent for cerebral lipids. This hypothesis, "the hydrate microcrystal theory," involves the interaction of the nonhydrogen-bonding anesthetic with water molecules in the brain. Pauling proposes that hydrate microcrystals, similar in structure to known hydrate crystals of chloroform, xenon, and other anesthetics may entrap ions and electrically charged side chains of protein molecules. This in turn decreases the energy of the electrical oscillations of the brain. Thus consciousness is lost. The striking correlation between the anesthetic partial pressure of the agent and the partial pressure necessary to form hydrate crystals lends a measure of support to the hypothesis.

The investigations of Clements and Wilson (1962) showed that inert gases can interact significantly with lipoprotein membranes of living cells. Their presence may change the effective dielectric constant and permeability of plasmic membranes. Ion transport may also undergo alteration. Mitochondrial membranes may be affected and thus enzymic activity, *viz.*, oxidative phosphorylation may be affected by a gaseous anesthetic. It thus appears that although the anesthetic is not metabolized and leaves the target cells as an intact molecule, its presence, through "gas hydrates," "microcrystals," or adsorption on lipoprotein membranes may produce profound cellular alterations.

These interesting studies of the physical properties of anesthetic agents have contributed useful information to our knowledge. But the key to the problem lies in a knowledge of what distortion of enzymic activity is provoked by their presence which causes a hiatus in consciousness.

Many studies have been designed to pinpoint the specific enzyme system which is reponsible for anesthetic action and the concomitant loss of consciousness. Numerous anesthetic agents have been shown to depress the oxygen uptake of brain brei. They exert little or no effect upon anaerobic glycolysis. It appears that in the process of the main line oxidation, anesthetic agents interfere with a sensitive flavoprotein which connects the phosphonucleotide dehydrogenase system with the cytochromes. The depression is reversible.

It has become apparent that there are many ways in which anesthetic agents can exert their action at an enzyme level and produce unconsciousness. Further, all agents which evoke anesthesia do not affect the same target enzyme system. Brody and Bain (1951) demonstrated that certain barbiturates, in anesthetic concentrations, uncoupled oxidation from phosphorylation in the mitochondrial fraction of rat's brain. Hulme and Krantz (1955) showed that ether produced the same effect in anesthetic concentrations.

Since the high energy phosphate bonds of adenosine triphosphate (ATP) are necessary for the synthesis of acetylcholine, a diminution of ATP would result in a paucity of acetylcholine necessary for neuronal transmission. However, xenon, which produces anesthesia when inhaled, was shown by Levy and Featherstone (1954) to be incapable of uncoupling oxidation from phosphorylation. On this enzyme system nitrous oxide was also inert. Nevertheless, nitrous oxide was shown to inhibit anaerobic glycolysis and also depress certain facets of the hydrogen transport system.

Thus it is clear that the precise mechanism of anesthesia at an enzyme level has not been demonstrated. The enzymic activities responsible for consciousness appear so complex and intricately interdependent that an agent influencing one facet of the system concomitantly affects the harmonious function of the whole. Besides, it seems likely that the anesthetic agents in use affect the enzymic activity of brain at different links in the complex chain of consciousness.

In summary, it appears that our present knowledge permits the following generalizations:

1. The use of the Overton-Meyer theory as a statement of anesthetic distribution in the body.
2. The presence of the agent in the central nervous system attacks the "main line" oxidation in the cells of the central nervous system. The target enzymes for different anesthetics are not always the same.
3. Anesthetics have been shown to act on a flavoprotein connecting the phosphonucleotide dehydrogenases with the cytochromes. Certain agents uncouple oxidation from phosphorylation.
4. The enzymic inhibitions are reversible processes.
5. The physical properties of the anesthetic vapor, by virtue of "gas hydrate" or "microcrystal" formation or adsorption on lipoprotein membranes, may be responsible for enzymic changes, diminution of synaptic transmission, and other alterations of neuronal activity resulting in anesthesia.

## Some Practical Aspects of Anesthesia

**Clinical signs.** Clinically, the amount of time related to the administration of anesthetics may be divided into 3 different periods. The first period is preanesthesia and includes all events prior to the administration of the anesthetic. This includes physical examination and evaluation of the patient as an anesthetic risk. The preanesthetic medication and the best anesthetic for the patient's age and physical condition are determined. The anesthetic period, with its various stages and planes, is second. The depth of anesthesia is dictated by the type of surgery and the patient's physical condition. The third period is that of recovery. Most hospitals have well-staffed recovery rooms that monitor many physiologic parameters until the patient returns to a normal alert state. At this time the anesthesiologist is concerned with electrolyte balance, hemodynamics and postoperative analgesia. This period also includes observation of the patient through the convalescent stage. The proper management of these periods is important in the return to full health of patients undergoing anesthesia.

**Preanesthetic medication.** Preliminary sedation of the patient prior to surgical anesthesia is a generally-accepted procedure. Preoperative apprehension is allayed. The patient accepts the anesthesia with less resistance. The induction stage is therefore smoother and less distressing to the patient. The number of drugs used by most anesthesiologists for this purpose is small. Many have been tried, but few have stood the test of repeated trial in the hands of different clinicians. The following general considerations may serve in premedication of various patients.

1. The physical condition of the patient is a factor. A muscular, well-developed patient needs more sedative, usually, than a slightly built patient. Debilitated patients require a smaller dosage. Excessively obese people need less than a patient of equal weight who is not obese.
2. Women usually need less sedation than men.
3. The anxious patient needs more sedation than the phlegmatic one.
4. The patient who is to be awake (spinals, regionals) usually needs more sedation than the one who is to be unconscious.
5. It is important that respiratory depression be avoided in certain operations, *e.g.*, chest cases.
6. The patient to be given thiopental should not be oversedated.

The most generally used preanesthetic drugs are:

1. The barbiturates with scopolamine or atropine
2. Morphine with atropine

3. Meperidine with atropine
4. Chlorpromazine

The barbiturates provide excellent sedation for anesthesia. For this purpose the rapidly-acting barbiturates are the drugs of choice. *Secobarbital* and *pentobarbital* 0.1 to 0.2 gm. are very suitable. The former appears to act somewhat more quickly than the latter. Neither of these drugs depresses salivation. Therefore, if ether is to be the anesthetic agent, it is advisable to give hypodermically 0.65 mg. of atropine sulfate to depress salivation. It is mentioned under thiopental anesthesia that a small dose of thiopental may be used intravenously instead of a barbiturate administered orally.

A subcutaneous injection of 15 mg. of *morphine sulfate* with 0.65 mg. of *atropine sulfate* provides sedation and depression of saliva flow.

*Scopolamine* potentiates the action of morphine on the central nervous system. On the parasympathetic division of the autonomic nervous system it resembles atropine in its action. Therefore, with scopolamine a smaller dose of morphine is effective and atropine may be omitted. Subcutaneously, 10 mg. of morphine sulfate is injected with 0.4 mg. of scopolamine hydrobromide. The combination produces a euphoria and prepares the patient for the anesthetic. Certain anesthesiologists prefer a combination of secobarbital and scopolamine. It appears from the studies of Orkin *et al.* (1956) that atropine produces the more intense and persistent cardiovagal block, and scopolamine the more intense and rapid extracardiovagal block. These investigators confirmed also the sedative action of scopolamine by electroencephalographic studies.

Eckenhoff and Helrich (1958) obtained data using morphine, meperidine, alphaprodine, secobarbital, and saline solution as preanesthetic agents in 1400 surgical patients. Secobarbital produced a higher proportion of calm, carefree, yet alert patients than did any of the narcotics employed. The narcotics were responsible for drowsy or sleeping patients with a higher incidence of apprehension. In addition, undesirable side effects were more frequently encountered in patients with narcotic premedication than with secobarbital.

**Anesthesia and asphyxia.** It should be clearly understood that anesthesia is not a phase of asphyxia when this term is used in its ordinary sense. Anesthesia ensues when the blood and central nervous system are completely oxygenated. Furthermore, such agents as the inert gases, nitrogen and helium, do not produce the anesthetic syndrome. It is true that by the inhalation of these agents to the exclusion of oxygen, unconsciousness is produced. The syndrome produced is essentially one of anoxia. On the other hand, deep surgical anesthesia can be brought about within a few minutes by the inhalation of 96 per cent oxygen and 4 per cent chloroform vapor.

It is striking indeed that in anesthetic concentrations the volatile anesthetics affect mainly the central nervous system. The specificity is significant. In higher concentrations the heart, liver, and other viscera are affected. But in the main, even though a profound hiatus in consciousness is produced, the action is confined principally to the central nervous axis.

**Analeptic drugs in anesthesia.** If anesthesia should proceed to the stage of threatened respiratory paralysis, there are certain measures which may be instituted to combat respiratory failure. If the anesthetic is a volatile agent, the anesthetic is withdrawn immediately and forced breathing with a mixture of 5 per cent carbon dioxide and 95 per cent oxygen or oxygen alone instituted. Carbon dioxide exerts a stimulating action on the respiratory centers provided the centers have not become insensitive to its effect by prolonged apnea. The further administration of carbon dioxide may be dangerous by leading to further respiratory depression. When respiratory failure prevails, there is an increase in blood carbon dioxide and a decrease in oxygen content. Artificial respiration with oxygen appears to be the key to success in resuscitation until the carbon dioxide content of the blood has been diminished. When the patient is well ventilated, the carbon dioxide-oxygen mixture may be employed to stimulate the respiratory centers.

Analeptic drugs may be simultaneously employed. *Nikethamide* (Coramine) appears to be the choice of many clinicians. The drug is available in 25 per cent solution; 2 to 3 ml. is administered intravenously to achieve the best results. The drug is rapidly detoxified and subsequent doses may be administered.

*Pentylenetetrazol* stimulates the respiratory centers and is also used for medullary stimulation in respiratory paralysis resulting from anesthesia. The drug is available in 10 per cent aqueous solution, and 1 to 3 ml. are administered intramuscularly, subcutaneously, or intravenously. The best results are obtained from the intravenous use of the drug.

For barbiturate respiratory depression (thiopental sodium) nikethamide has a specific antagonistic effect upon the depressed centers. Ritalin is another cerebral stimulant which is used to awaken patients from deep barbiturate depression (page 479).

*Epinephrine* and *amphetamine* may be employed if the blood pressure is low. The latter drug is also an effective respiratory stimulant. In cases of cardiac failure the injection of epinephrine and cardiac massage are the most effective restorative measures (Kay, 1951). If this fails to restore the heart, MacKay *et al.* (1951) recommend the injection of 2 to 4 ml. of 10 per cent solution of calcium chloride into the left ventricular cavity. If ventricular fibrillation should occur, shocking the heart directly with electrodes from the defibrillatory apparatus is advocated. A series of short shocks of 110-volt current is employed. If the shock does not defibrillate the heart, the the surface of the organ may be sprayed with 3 to 5 ml. of 1 per cent procaine hydrochloride solution.

Jude *et al.* (1961) reported a new method of producing artificial circulation by external sternal compression without thoracotomy. In 138 cardiac arrests from various causes including anesthesia, 60 per cent were returned to their prearrest central nervous system and cardiac status.

**Hypotension and surgical hemorrhage.** In surgery of the brain and other very vascular areas, the production of hypotension will greatly diminish bleeding and facilitate the surgical procedure. The drug Arfonad, a ganglionic blocking agent, has been used for this purpose. With halothane anesthesia the blood pressure may be lowered, and it appears that the necessity for the use of Arfonad has passed. Arfonad is discussed on page 530 of the 5th edition.

**Convulsions under anesthesia.** Occasionally convulsions occur under the volatile anesthetics. These are not the tremors that are frequently seen in early divinyl oxide and ether anesthesia but are generalized convulsive seizures which may occur under surgical anesthesia. They are a serious anesthetic complication.

The onset of the convulsion may start with a few twitches of the facial muscles. These extend rapidly to the extremities and a prompt succession of tonic convulsive seizures soon supervenes, involving the entire body.

The origin of these convulsions is not definitely established, and undoubtedly no one cause can be isolated as the prime factor in all types of anesthetic convulsions. Overdosage of the anesthetic agent has been suggested as one of the causes because of the fact that convulsions generally occur during deep anesthesia. Impurities in ether have been blamed for ether convulsions. The facts, however, discredit this hypothesis. Lindgren's (1946) studies using ether with aldehyde and peroxides as impurities did not show these substances to produce muscle spasm. They produced only a delay in the onset of anesthesia.

The convulsions appear to occur most frequently in young individuals who at the time of anesthesia are suffering from infection, producing a hyperpyrexia.

Owens *et al.* (1956) demonstrated in dogs that ether anesthesia and hyperthermia produced severe electroencephalographic abnormalities. With thiopental anesthesia and hyperthermia these changes did not occur. The behavior of the dogs under ether anesthesia with hyperthermia showed a striking similarity to the clinically observed ether convulsion. These findings are in accord with the clinical observation that ether convulsions occur most frequently in the hyperpyrexic patient.

Other factors which may contribute to anesthetic convulsions are:

1. Carbon dioxide-oxygen imbalance
2. Calcium deficiency
3. Cerebral congestion

In the authors' opinion the character of the anesthetic agent appears to be the predisposing factor. *Propethylene ether* prepared and studied by us showed excellent possibilities as a clinical anesthetic agent. In human anesthesia this was confirmed in about 100 cases (Ruth, 1943). Then there occurred an exceedingly high incidence of convulsions during deep anesthesia. This was confirmed in other clinics. A comparison of the occurrence of convulsions under ether in these clinics with those under propethylene ether definitely pointed to the agent as predisposing the patient to convulsions.

The treatment of the anesthetic convulsion must be promptly instituted. Hewer (1946) gives the following procedure:

1. Raising the patient's head and if necessary having him sit upright.
2. Sponging the face and limbs with cold water.
3. Momentary compression of the common carotid arteries to diminish the congestion of the Rolandic area.
4. Thiopental sodium should be injected cautiously by vein. The barbiturate should be given slowly and the smallest effective dose used. Otherwise it may precipitate circulatory and respiratory depression of a serious nature.

**Anesthetic explosions.** *Ethylene*, *cyclopropane*, and *ethyl ether* are flammable. When mixed with oxygen the gas mixtures are highly explosive. The explosion rates with these 3 anesthetics are 2 to 4 per 100,000 anesthesias; the mortality rate is 1 in 150,000 (Woodbridge, 1939). Anesthetic explosions are definitely diminishing. The reasons for this are clear. First, ethylene is seldom used and the use of ether is diminishing. The fluorinated anesthetics, which are being used widely now, present no explosion hazard. Second, there is an acute awareness of the danger of explosions, especially with cyclopropane, and static electric discharge is meticulously avoided when cyclopropane or ether are employed. When mixed with oxygen, the lower limit of flammability of cyclopropane is 2.4 per cent; with ether it is 2.1 per cent.

**Anesthesia mortality data.** Reliable data on anesthetic mortality are very difficult to obtain. The question of "bad anesthetic risks" confuses the statistics. Besides, not all anesthetic deaths are reported. Beecher and Todd (1954) made a comprehensive study of anesthetic deaths involving more than one-half million anesthesias administered in several university hospitals. They admit that the definition of an anesthetic death must of necessity be arbitrary. The participants in this study considered such cases as anesthetic deaths where it was agreed that anesthesia was an important factor in the death of the patient.

They found the over-all death rate to be 1:1560. Other data are most revealing in this study. For example, when muscle relaxants were used the death rate increased 6-fold over those cases which did not involve the use of these agents. There was no evidence found from the data that the experience or training of the anesthesiologist protected the patient from disaster with the muscle relaxants. They conclude from these studies that the muscle relaxants should be used only when a clear advantage can be achieved by their use. They should not be used for "trivial purposes or as a corrective for generally inadequate anesthesia." Evidence indicated that curare is more dangerous with ether or cyclopropane than when used with thiopental sodium.

This comprehensive study involved the use of *d*-tubocurarine only as a muscle relaxant. Succinylcholine chloride is used today almost to the exclusion of other relaxants. It appears to be much safer and besides, anesthesiologists have acquired more skill through experience in the proper use of muscle relaxants. It appears that such a study conducted today would reveal far less danger involved in the use of muscle relaxants than indicated in the Beecher and Todd survey.

Beecher and Todd (1954) extrapolated their figures to the approximately 8 million cases of surgical anesthesia in America each year, and their anesthetic deaths were 5128. This provocative study indicates that despite the great advances that have been made in this field the death rate is high, and better agents appear to be warranted.

In another review of 589 cases in which anesthesia played a role in the death of the patient, 110 deaths were due to vomiting or regurgitation. Further, 110 deaths were due to circulatory failure immediately following a barbiturate injection. It appears that in a large number of the deaths the cause was quite clear, and the majority of cases occurred after departures from accepted practice.

## THE INDIVIDUAL VOLATILE ANESTHETICS

### Nitrous Oxide, U.S.P. $N_2O$.

Nitrous oxide is a colorless, odorless gas. It is claimed by some to elicit a sweet taste. One liter of the gas at S.T.P. weighs 1.977 gm. Metals will not rust in dry nitrous oxide. The gas does not support combustion unless the molecule disintegrates into the elements nitrogen and oxygen. It is the latter that supports combustion. Seeds cannot germinate in an atmosphere of the gas. Nitrous oxide does not combine with hemoglobin.

Nitrous oxide is very soluble in water. The gas enjoys a high solubility in blood. Blood will dissolve approximately 45 volumes per cent of nitrous oxide. Twenty-five to 30 volumes per cent in the blood produces anesthesia. Although the solubility of nitrous oxide in aqueous fluids is high, it is exceeded by its oil solubility. This permits the agent to partition out of the blood into the lipids of the central nervous system. The oil/water coefficient of nitrous oxide is approximately 3.

**Anesthesia with nitrous oxide.** Nitrous oxide is administered in a circuit mixed with oxygen by the semi-closed technic. Exceptionally high concentrations of the gas in the inhaled air are required to produce surgical anesthesia. In fact, this cannot be accomplished without dangerous hypoxia. Table 22-2 shows the effect of nitrous oxide mixed with various percentages of oxygen.

The induction period is short and not unpleasant. By inhalation of the gas-oxygen mixture for 30 to 90 seconds, the patient becomes lightly anesthetized. The induction is frequently accompanied by laughter and hilarity and hence the name "laughing gas." The gas is not irritating to the membranes of the nose or mouth and hence can be respired without coughing caused by local irritation.

During anesthesia with nitrous oxide, the patient frequently experiences dreams of a very vivid nature. Sometimes these are voluptuous in character, and it is always advisable for the physician or dentist to have an assistant present when nitrous oxide is administered.

The light anesthesia produced by nitrous oxide limits its field of usefulness. With 85 to 90 per cent of the gas with oxygen, abdominal relaxation cannot be obtained. The legs and arms are likewise not completely relaxed. However, dental operations can be performed without pain safely under anesthesia with the gas.

Recovery occurs almost immediately when the anesthetic mask is removed.

**The effect of nitrous oxide on brain metabolism.** Hosein *et al.* (1955) studied the problem selectively on the various segments of the metabolic pathways of the rat's brain. Using rat's brain slices, they observed a slight inhibition of oxygen consumption when a mixture of $N_2O$ 80 per cent and $O_2$ 20 per cent was used. The addition of various substrates enhanced the inhibitory effect of nitrous oxide. These investigators found that nitrous oxide significantly inhibited anaerobic glycolysis in the tissue. The phosphorylation of glucose was unaffected by nitrous oxide. However, in the hydrogen transport system, cytochrome b of the succinoxidase system and the flavoproteins, diaphorase, and TPN-cytochrome c-reductase were sensitive to the nitrous oxide gas mixture. This study establishes a basis for the anesthetic activity of nitrous oxide at an enzyme level.

TABLE 22-2

*Nitrous Oxide Anesthesia*

| Concentration Nitrous Oxide | Concentration Oxygen | Anesthetic Syndrome |
|---|---|---|
| 80 | 20 | Blurred consciousness and analgesia |
| 86 | 14 | Complete analgesia |
| 89 | 11 | Light anesthesia |
| 94 | 6 | Complete anesthesia |

**Advantages and disadvantages of nitrous oxide.** The principal uses of nitrous oxide as an anesthetic are as follows:

1. To induce anesthesia to be followed by ether
2. For short dental operations
3. To supplement anesthesia with thiopental sodium
4. For obstetric analgesia (80 to 90 per cent with oxygen)
5. To provide a state of unconsciousness during surgery under spinal anesthesia

When nitrous oxide is employed in sufficient concentration to produce abdominal relaxation, dangerous hypoxia occurs. In fact, whenever nitrous oxide is used to produce an anesthetic syndrome beyond the stage of analgesia, less oxygen is present with the gas than is present in the atmosphere. Oxygen deprivation is one of the greatest dangers in anesthesia.

The excitation in the induction stage with nitrous oxide, although short, is sometimes rather violent. In patients with severe hypertension this is dangerous since the release of endogenous epinephrine tends to aggravate the condition.

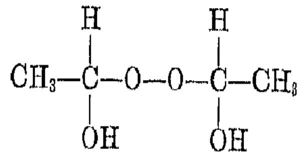
Nitrous oxide is an extraordinarily harmless type of gas. It has no effect upon excised tissues. Dogs have been kept anesthetized by the gas for 72 hours without apparent harmful effects. The medullary centers, circulation, blood chemistry, blood cells, and other functions of the body are not significantly influenced by anesthesia with nitrous oxide. This, of course, is true provided that hypoxia has not been permitted to supervene for any considerable period of time.

The gas is eliminated mainly in the exhaled air within 2 to 3 minutes after the removal of the mask. Nitrous oxide is not metabolized in the body.

### Ethyl Ether, U.S.P. $(C_2H_5)_2O$

Ethyl ether is a colorless mobile liquid with a characteristic odor. It is very volatile, and its vapors are flammable. Ether boils at 35°C.; its specific gravity is about 0.714 at 25°C. Anesthetic ether contains from 96 to 98 per cent of diethyl oxide; the remainder consists of alcohol and water. Ether dissolves in about 12 volumes of water. It is soluble in oils and in the immiscible solvents.

Ether used for anesthetic purposes is required to be free from aldehyde and peroxides. The latter are believed to be irritating to the bronchial tree. Lindgren (1946) showed that small quantities of peroxide present in ether delayed the onset of anesthesia with the agent. The peroxide forms when ether is exposed to light and air. Ether peroxide is dihydroxydiethyl peroxide, bis-($\beta$-hydroxyethyl) peroxide, as shown in the formula:



$$CH_3-\overset{H}{\underset{OH}{C}}-O-O-\overset{H}{\underset{OH}{C}}-CH_3$$

Pure ether ignites at 190°C. With quantities of peroxides present ether may ignite at a temperature as low as 100°C.

The peroxide formation in ether has been the subject of many investigations and controversies (Gold, 1934). To avoid peroxide formation the Pharmacopeia requires that anesthetic ether be preserved in tight containers of no more than 3 kg. Further, it should not be used for anesthetic purposes if it has been withdrawn from the original container longer than 24 hours. The Pharmacopeia permits anesthetic ether to be shipped in larger containers for repackaging in smaller containers as previously stated; it is required that the ether meet the official requirements at the time of repackaging.

**Anesthesia with ether.** Ethyl ether is one of the most generally used of all volatile anesthetics. It is not decomposed in the body, but its presence in the cells of the central nervous system produces insensibility to pain and a hiatus in consciousness. It requires 3 to 5 per cent concentration of ether in the inspired air to produce anesthesia. During surgical anesthesia the concentration in the blood is approximately 100 to 150 mg. per cent. The blood pressure remains essentially normal, and respiration is full and regular during ether anesthesia. The relaxation of the abdominal musculature is excellent. The administration of the anesthetic agent in the circuit with oxygen instead of air reduces the incidence of postanesthetic nausea and vomiting.

The vapors of ether are irritating to the respiratory tract. This produces the flow of mucus, and atropine is desirable as premedication in ether anesthesia. The induction period is long and often stormy and harrowing to the patient. If the anesthesiologist used 3 to 5 per cent ether in the inspired air, the induction period might take as long as 20 minutes. Concentrations of 20 to 30 per cent are used to shorten the induction period. These concentrations of ether are irrespirable in some people and produce severe choking and even laryngeal spasm. All of this disagreeable phase of ether anesthesia is minimized by the use of nitrous oxide-oxygen mixtures for rapid and smooth induction. When the patient is well under nitrous oxide, ether vapor is gradually allowed to replace the former.

Obviously the potency of ether vapor as an anesthetic permits excellent oxygenation of the patient. With 3 or 5 per cent of ether in the inspired air the patient may receive 97 or 95 per cent of oxygen during the anesthesia. This avoids all dangers of hypoxia and diminishes postoperative sequelae such as nausea and vomiting.

Eger *et al.* (1962) studied the uptake of ether by the body tissues of man and its distribution by injecting intravenously a 5 per cent V/V ether solution. A constant arterial blood level was maintained by monitoring the electroencephalogram pattern. The uptake of ether vapor by the tissues was 900 ml. per minute during the first 5 minutes with a rapid fall to about one-half this value in the second 5 minute period. The uptake of ether gradually diminished; after 60 minutes the amount was 180 ml. per minute. This more recent study using the electroencephalogram pattern as a criterion of the arterial blood level appears to correlate well with data on blood levels of ether in dogs using the inhalation technic and chemical assays of ether in the blood.

Ether anesthesia may proceed for 3 to 4 hours without serious harm to the patient. Relaxation in most individuals is excellent. Breathing is regular and often stertorous. The elimination of ether from the body is slow. The patient recovers from anesthesia of 40 to 60 minutes within 20 to 30 minutes. Mucus discharge and nausea frequently accompany the awakening of the patient.

**The effect of ether on the respiration.** In the early stages of anesthesia, ether markedly stimulates the respiration. The principal cause of respiratory stimulation appears to be reflex in character and is the result of passage of irritating ether vapor over the trachea and bronchi. Exposure of the respiratory tract to ether above the larynx evokes apnea. Other factors that may contribute to the respiratory stimulation of ether are the release of catechol amines and the production of metabolic acidosis. In surgical anesthesia, the respiration is deep, often stertorous, and regular. Upon further increasing the concentration of ether in the blood the centers of respiration are depressed, and ether can produce respiratory arrest. The respiratory arrest with ether, especially in the early stages, is easily overcome by artificial respiration.

**The effect of ether on the circulation.** For the most part the heart is unaffected by anesthetic concentrations of ether. The pulse is either normal or somewhat accelerated. There are occasional varied arrhythmias. These generally occur in the early stages of induction and are probably the result of excitation rather than the direct effect of ether. Myocardial contractility is somewhat reduced during ether anesthesia as was demonstrated by Price and Helrich (1955) using the dog heart-lung preparation. The blood pressure remains normal or is slightly elevated in light surgical anesthesia with ether. When the stage of threatened collapse is reached, the blood pressure falls. Bleeding time is unchanged under ether anesthesia although the clotting time of blood is somewhat decreased.

The effect of ether on the frog's heart *in situ* is shown in figure 22-1. This concentration, 0.14 M, is nearly 10-fold the anesthetic concentration of 125 mg. per cent.

Bonnycastle (1942) showed that ether anesthesia slightly diminishes the plasma volume when morphine and atropine are used for premedication.

The tachycardia which frequently occurs during ether anesthesia results from vagal depression.

Pertzoff and Gemmill (1949), using human erythrocytes, demonstrated that their phosphorus uptake was retarded by the presence of ether *in vitro*. $P^{32}$ tracer technic was employed. Sodium barbital shared this effect with ether.

Price *et al.* (1959) made an interesting contribution to the anesthetic syndrome induced by ether and other agents. They studied the release of norepinephrine into plasma as an indication of augmented sympathetic nervous system activity. Ether produced erratic increases in norepinephrine release. Cyclopropane produced an increase in norepinephrine plasma levels which paralleled the depth of anesthesia. Thiopental and halothane anesthesia evoked little or no changes in plasma norepinephrine levels. These findings are of interest in the choice of an anesthetic for a patient with pre-existing cardiac arrhythmias.

The circulatory changes occurring in patients in the light planes of ether surgical anesthesia were measured by Kubota *et al.* (1962). The blood pressure, pulse rate, cardiac output, and peripheral resistance showed no significant alterations. The only definitive change was an increase in

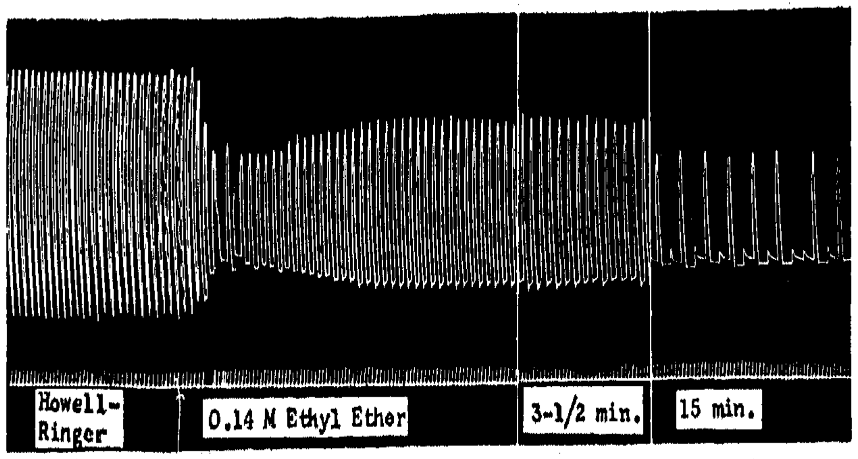


Fig. 22-1. Ether on the Frog's Heart
(From Krantz, J. C., J. Pharmacol. & Exper. Therap., 69: 207, 1940.)

central venous pressure. The authors suggest that this change might indicate a "state of myocardial incompetence." It is emphasized that the release of catecholamines during ether anesthesia may exert varying degrees of influence upon the hemodynamics of ether anesthesia.

**Effect of ether on metabolism.** Under ether anesthesia metabolism is depressed in general. Glucose increases in the blood as a result of its decreased utilization in the periphery and mobilization of hepatic glycogen as glucose owing to the release of catecholamines. Serum lactate is also increased as is nonprotein nitrogen in the blood.

**The liver under ether anesthesia.** There is a slight and readily reversible change in hepatic function during ether anesthesia, as shown by the Bromsulphalein test. Bile secretion is also diminished. Liver glycogen is decreased (50 per cent in the first hour) and then gradually thereafter. No characteristic histologic changes are seen in the liver after ether anesthesia.

Fairlee *et al.* (1951) compared the livers of patients undergoing anesthesia with ether, cyclopropane, and spinal agents using a battery of liver function tests. Bromsulphalein, hippuric acid excretion, serum bilirubin, Quick prothrombin time, urine urobilinogen, serum alkaline phosphatase and serum cholesterol, and cholesterol esters were measured preoperatively and on the 1st, 3rd, and 5th postoperative days. Nearly all of the patients exhibited some abnormality in one of the tests. However, there were no differences among those subjected to the 3 anesthetic agents.

Comparing the effect of ether and chloroform on the liver during repeated anesthesias, Evans *et al.* (1945) anesthetized dogs by the open drop method for 2 hours on 3 consecutive days. Three days after the last anesthesia the animals were sacrificed, and histologic studies were made of their livers. Ether produced no demonstrable pathologic changes. Chloroform, on the other hand, produced fatty degeneration in the livers of all animals studied. The changes were most marked in the central portion of the lobules.

**The kidneys under ether anesthesia.** The kidney is not markedly affected by ether anesthesia. As a rule, phenolsulfonphthalein excretion is not altered significantly. During anesthesia the urine output is reduced. This is believed to be due to the release of the anti-diuretic hormone from the pituitary. Frequently the urine will show protein after ether anesthesia. Acetone and diacetic acid are sometimes present in the urine.

Beecher and associates (1948) studied the effect of ether and cyclopropane anesthesia on renal function in man. The renal clearances of mannitol and sodium *p*-aminohippurate were determined before and during anesthesia. All patients showed normal renal function when the study was instituted. All of the subjects under both types of anesthesia showed a diminution in glomerular filtration rate and effective renal plasma flow. The average urine flow was lowered in each group of patients. The changes were qualitatively similar, but quantitatively they were greater with cyclopropane. These workers assert that their findings combine the effect of trauma of the operation and the anesthesia simultaneously on renal function. Their previous work with ether showed no significant renal changes in the absence of shock. These studies indicate that in patients where shock is present or may be anticipated during the operation, ether is preferable to cyclopropane as an anesthetic.

Beecher and his associates (1950) restudied the problem of incipient acidosis under ether anesthesia. Van Slyke *et al.* (1922) reported that ether anesthesia produced varying degrees of acidosis in dogs. These findings were assumed to obtain in man. Beecher determined the pH and $CO_2$ content of arterial blood in 20 surgical patients. Fixed acid changes were also determined on most of the subjects. Ether was administered by the open drop method and by the closed system with nitrous oxide and oxygen, and the determinations were repeated at the end of the operation. There were no significant variations in pH of arterial blood, $CO_2$ content, or fixed acid in patients who received ether alone. With nitrous oxide-ether anesthesia there was a slight rise in fixed acid, which was not clinically significant. It appears, therefore, that ether anesthesia does not produce acidotic changes in the human as shown by these carefully controlled studies. Beecher suggests that the anesthetic technic employed by Van Slyke with his dogs might have been responsible for the incipient acidosis.

**The effect of ether on skeletal muscle.** Ether produces excellent skeletal muscle relaxation. It has been demonstrated that ether elicited a curare-like effect. When a sufficient concentration of ether is present at the neuromuscular junction, the action of acetylcholine is blocked. As ether anesthesia reaches deeper planes the concentration of ether at the neuromuscular junction increases and reaches a concentration effective in

inhibiting the action of acetylcholine. In deep ether anesthesia the intensity of motor impulses reaching the neuromuscular junction is progressively diminished. Therefore, the quantity of acetylcholine released at the neuromuscular junction is also reduced. This is likely the more effective of the 2 factors involved in the curare-like action of ether. When ether anesthesia reaches the level of bulbospinal status, the quantity of acetylcholine released at the neuromuscular junction of skeletal muscle is quite small. Further, that which is released is blocked by an effective ether concentration and a curare-like flaccid paralysis of skeletal muscle occurs. At this stage all skeletal muscle, except the crural fibers of the diaphragm, is without tone. No other commonly used anesthetic exhibits this curare-like action. Therefore, when neuromuscular blocking agents are to be used during ether anesthesia, extreme caution must be exercised, and the recommended dose is usually reduced to one-half that employed with other anesthetic agents.

**Ether analgesia.** Analgesia elicited by ether was described first by the English investigator John Snow in 1847. Gwathmey (1921) revived the use of ether analgesia by administering the agent rectally in oil. He believed this to be the safest and most physiologic manner in which to administer ether. The recent increase in cardiac surgery called for an anesthesia that would provide a better surgical risk than the deeper stages of ether anesthesia. Accordingly, Artusio (1954) studied with modern equipment the detailed planes of stage I of ether anesthesia. He found these could be subdivided into 3 distinct planes that were determined by questioning the patient and estimating the response to pain stimuli. Stage I, plane 3, was found to be the most physiologic level of ether anesthesia. Delirium and reflex activity were abolished by the following technic.

Bellville and Artusio (1955) recommend premedication with 0.2 mg. of atropine sulfate 1 hour prior to anesthesia. Following 75 to 100 mg. of thiopental sodium intravenously, ether anesthesia was induced following nitrous oxide and oxygen. The patient was carried down to stage III, plane 1, and then allowed to lighten until there was response to the spoken word. At this degree of ether analgesia the average concentration of ether in the venous blood is only 10 mg. per cent. Electroencephalogram voltages of the fully-awake patients fell within the range of 20 to 60 microvolts, with predominant frequencies of 8 to 18 cycles per second. During ether analgesia the voltage was unchanged, but the frequency of discharge was nearly doubled.

Many major surgical procedures have been conducted under ether analgesia. The stability of blood pressure and pulse rate, full oxygenation of the patient, and little interference with autonomic balance appear to be special features of this type of narcosis.

**Advantages and disadvantages of ether.** The widespread use of ether as a general anesthetic bespeaks the fact that its advantages far outweigh its disadvantages. Ether boils at a low temperature and is difficult to administer in tropical temperatures. Its vapors are flammable and somewhat irritating to mucous membranes. The potency of ether is low, comparatively speaking, and its induction period is slow and often stormy. These difficulties are obviated by the use of other agents for induction. Postanesthetic gastrointestinal distress is another disadvantage of ether.

On the other hand, ether is a safe anesthetic. Its principal site of action is the central nervous system. As has been shown, the circulation is not significantly affected by anesthetic concentrations of ether in the blood. Ether is sufficiently potent to permit the use of high concentrations of oxygen in the inhaled anesthetic mixture. The abdominal relaxation provided by ether is good. It is inexpensive, and when stored properly it is comparatively stable. Although ether has been replaced to a large measure with the newer fluorinated anesthetics, it appears destined to be with us for a long time. Dodd (1962) states, "Of the potent general anesthetic agents, ether fits the biologic and statistical requirements as well as any and better than most according to data now available."

**Vinyl Ether, U.S.P.** $(CH_2{:}CH)_2O$. This compound is also called "Divinyl Oxide" and "Vinethene." It occurred to Leake (1930) that it would be of interest to prepare a hybrid molecule between ethyl ether and ethylene, that is, a molecule which contained the essential features of

| $C_2H_5OH$ | $C_2H_5{-}O{-}C_2H_5$ |
|---|---|
| Ethyl Alcohol | Ethyl Ether |
| $CH_2{=}CH_2$ | $CH_2{=}CH{-}O{-}CH{=}CH_2$ |
| Ethylene | Vinyl Ether |

molecules of each of these anesthetics. Following this suggestion, Major and Ruigh (1931) prepared vinyl ether. The relation of these compounds to ethyl alcohol can be seen from the accompanying formulas. Vinyl ether is a clear, colorless, very volatile and flammable liquid, sp.gr. about 0.77. Its odor is characteristic and disagreeable to many individuals; 3.5 per cent of alcohol is added to the liquid, and the resultant solution boils between 28 and 31°C. Polymerization is prevented by the addition of 0.01 per cent of phenyl-α-naphthylamine.

Vinyl ether is more powerful than ethyl ether. With it anesthesia is rapidly induced. Indeed, the planes of anesthesia are passed through so rapidly that great care must be exercised to ascertain the depth of anesthesia. Because of injury to the liver which may occur upon prolonged inhalation of this anesthetic agent, its use is confined to operations of short duration. It is especially useful for dental procedures. In dogs, divinyl oxide produces cardiac fibrillation. This does not obtain in man.

**Ethyl Vinyl Ether.** Ethyl vinyl ether (*Vinamar*) was studied extensively as an anesthetic agent by the authors in 1947. We observed that this ether compared favorably as an anesthetic agent with divinyl ether and diethyl ether in various species of laboratory animals. After preliminary experiments on man, the agent was suggested for clinical trial. Vinamar has had extensive clinical trial by Sadove *et al.* (1955 *et seq.*) and Dornette and Orth (1955). It is now available as an inhalation anesthetic.

Vinamar is a colorless, mobile liquid with a characteristic ethereal odor. Its density is 0.759 and its boiling point 35.8°C. The oil-water coefficient of Vinamar is 45 ± 5. The ether is preserved by the addition of 0.01 per cent of N-phenyl-α-naphthylamine and 3 per cent of absolute ethanol.

The potency of Vinamar is intermediate between that of diethyl ether and divinyl ether. To illustrate, under controlled conditions in the dog, 0.30 ml./kg. of divinyl ether, 0.56 ml./kg. of Vinamar, and 1.1 ml./kg. of diethyl ether produce surgical anesthesia (Krantz *et al.*, 1947).

Dornette and Orth (1955) state that the agent produces "rapid onset of anesthesia with quick loss of consciousness." It was observed that Vinamar elicited excellent analgesia similar to trichloroethylene. Dornette *et al.* (1955) demonstrated the absence of hepatic toxicity under Vinamar anesthesia in the dog and man. Vinamar has a broad spectrum of utility in general anesthesia. It appears to be useful for inducing anesthesia. It is recommended for supplementing other anesthetic agents such as nitrous oxide. Further, it has been found valuable for general surgical procedures, affording excellent relaxation. Sadove *et al.* (1955) found that Vinamar was well tolerated by infants. Recovery from anesthesia with Vinamar is prompt. Further clinical experience with Vinamar will likely extend its scope in the ever increasing armamentarium of the anesthesiologist.

**Safety and structure of ethers as anesthetics.** In studies with various new anesthetics, Krantz *et al.* (1947) used the anesthetic index technic on the dog. In a series of 11 nonhalogenated ethers it was observed that anesthetic potency and potency in evoking respiratory arrest paralleled each other. The "margins of safety" for most ethers were found to be the same, with the exception of that for divinyl oxide. The margin of safety of this ether is approximately 0.5 that of diethyl ether. It was observed that potency paralleled the oil/water coefficient. High oil/water coefficients appear to be characteristic of ethers with unsaturated or cyclic alkyl groups.

## Chloroform, U.S.P. $CHCl_3$

Chloroform is a clear, colorless, highly refractive liquid. It has a sweetish odor and a burning, sweetish taste. It boils between 61 and 62°C.; its vapors are not flammable. The specific gravity of chloroform is 1.476 at 25°C. It contains about 1 per cent of ethyl alcohol. Chloroform is quite insoluble in water, but miscible with alcohol, oils, and the ethereal solvents in all proportions.

Chloroform for anesthetic purposes must be kept protected from light and air, otherwise decomposition will occur, forming the toxic *phosgene.*

**Anesthesia with chloroform.** Anesthesia may be induced with chloroform using the open drop method or rebreathing in a closed circuit. With either method it is desirable to use a high concentration of oxygen in order to reduce the likelihood of liver damage. The vapors of chloroform are as irritating to mucous membranes as those of ether, but the concentration required for induction and maintenance of anesthesia is so much less that chloroform vapor appears to be quite bland.

From 2 to 4 per cent of chloroform in the inspired air will rapidly induce anesthesia. The induction is not unpleasant. Light anesthesia can be maintained with 1.35 per cent in the inspired air, and deep anesthesia is produced by 1.65 per cent of chloroform.

The relaxation in chloroform anesthesia is excellent. The recovery from chloroform anesthesia is accompanied by less nausea and vomiting than from ether anesthesia. The concentration in the blood during anesthesia is about 13 mg. per cent.

**Chloroform on the respiration.** Chloroform depresses the respiration markedly. The thresholds to carbon dioxide of the respiratory centers are raised. The minute volume exchange is diminished. The bronchial musculature is relaxed.

**Chloroform on the circulation.** Chloroform is directly toxic to the myocardium. On the perfused heart of the frog the toxicity of chloroform to the heart is about 30 times that of ether. On the mammalian heart 50 mg. per cent chloroform produces injury, and 60 mg. per cent will reduce cardiac activity by 50 per cent.

The cardiac toxicity of chloroform is one of its principal disadvantages. The vapor of chloroform is engulfing when first inhaled. Reflexly, breathholding occurs. Then the patient takes a deep breath, and a high concentration of chloroform is carried to the lungs in the inspired air. This is carried to the left atrium, and intoxication of the myocardium occurs before the chloroform concentration is diluted by the general circulation. Indeed the concentration of chloroform in the blood in the left atrium may be 10 times the concentration in the right atrium in this stage of chloroform anesthesia.

There are other factors that embarrass the heart. Chloroform stimulates the vagus, which produces cardiac slowing. Simultaneously, through excitation in the induction period, epinephrine is secreted. This stimulates the cardiac accelerator mechanism. The combined effect of vagus stimulation and increased epinephrine release stimulating the myocardium through the cardiac accelerator predisposes the heart to ventricular fibrillation.

Hill (1932) showed that under chloroform anesthesias which were regarded as normal, the heart was subject to arrhythmias and extraventricular systoles of diverse origin. In a comprehensive study of chloroform anesthesia in man and animals, Waters (1951) found this agent capable of eliciting frequent cardiac abnormalities. Waters cautioned against the ever-present danger of direct or reflex cardiac depression which might proceed to arrest. Ventricular tachycardia was encountered in half of the patients. There was little tendency, however, to ventricular fibrillation.

The blood pressure may be lowered under chloroform anesthesia. This is the result of a 3-fold action of the agent:

1. Cardiac slowing
2. Depression of the vasoconstrictor center
3. Splanchnic vasodilatation

Waters (1951) did not confirm the gradual fall in blood pressure in 63 patients under chloroform anesthesia which is generally attributed to this agent. Indeed, some of his patients were under chloroform for 2 hours without appreciable alteration in blood pressure.

Chloroform diminishes the oxygen-carrying capacity of the red cell. Therefore, all tissues suffer from a varying degree of hypoxia during chloroform anesthesia.

**The effect of chloroform on metabolism.** Under chloroform anesthesia metabolism is decreased. Glucose increases in the blood as a result of the decreased utilization in the periphery and mobilization of hepatic glycogen as glucose from the release of epinephrine during the period of excitation. Nonprotein nitrogen in the blood is also increased.

**The liver under chloroform anesthesia.** In the study of the liver under ether anesthesia the toxic effects of chloroform on the liver were considered. Chloroform diminishes the dye excretion of the liver. Other liver function tests also show diminished liver efficiency after chloroform anesthesia. The glycogen content of the liver is rapidly depleted; three-fourths in the first half-hour and less rapidly thereafter. In animals, protection from the toxicity of chloroform on the liver is partially afforded by providing a high liver glycogen. Miller and Whipple (1940) demonstrated that the dog's liver was more vulnerable to chloroform intoxication when there is protein depletion of the animal. Plaa *et al.* (1958) studied the hepatotoxicity of a number of chlorinated hydrocarbons by measuring the prolongation of the pentobarbital sleeping time. The hydrocarbons were injected subcutaneously in oil solution. Chloroform was shown to be one of the most hepatotoxic of all of the chlorinated hydrocarbons tested. Its toxicity was exceeded only by that of carbon tetrachloride.

Jones *et al.* (1958) used chloroform and other volatile anesthetics dissolved in olive oil and administered them to white mice by esophageal instillation. After 72 hours histologic studies were made of the liver to determine hepatotoxicity. Frank necrosis was found only after chloroform and divinyl ether. Halothane produced fatty infiltration without necrosis. Ethyl ether was the least hepatotoxic of all of the anesthetics tested.

The autopsy findings in the liver after chloroform poisoning reveal fatty degeneration, necrotic areas in the lobules, and scattered hemorrhages. Occasionally yellow atrophy of the liver has been seen.

Delayed chloroform intoxication occurs sometimes 1 or 2 days after the patient has been anesthetized with this agent. The onset of the syndrome is similar to that of diabetic acidosis. There is nausea and vomiting with drowsiness and malaise. Acetone and diacetic acid are present in the urine. The carbon dioxide-combining power of the blood is lowered. Coma and death may follow. Autopsy usually reveals extensive liver and some kidney damage.

It appears that frequent hepatic damage after chloroform anesthesia may well be due partially to faulty technic during anesthesia, *e.g.*, hypoxia or excessive concentrations of chloroform in the blood. Waters (1951) found no case of "delayed chloroform poisoning" in 121 patients anesthetized with the agent. Using controlled groups of patients under other anesthetic agents, this investigator found some hepatic dysfunction in 52 per cent of the patients who had received chloroform and 42 per cent of the individuals who had been anesthetized with other agents.

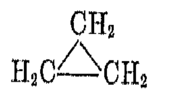
Dobkin *et al.* (1960) found chloroform to be a safe anesthetic when used with a modern temperature-compensated vaporizer. They were able to achieve surgical anesthesia with less than 1 per cent chloroform in the inhaled gas stream. Later, these authors stated that meticulous care must be used to maintain oxygenation and prevent retention of carbon dioxide. Poe and Mayfield (1960) used chloroform with success in 70 patients requiring a nonflammable anesthetic. They avoided hypercarbia and controlled the chloroform concentration. Patients without liver disease were selected.

**The kidneys under chloroform anesthesia.** Kidney function is depressed by chloroform anesthesia. Proteinuria occurs in about 30 per cent of all patients subjected to chloroform anesthesia. Acetone occurs often in the urine. The excretion of urine is completely stopped during anesthesia. Polyuria persists after recovery.

**The advantages and disadvantages of chloroform.** In the authors' opinion the disadvantages of chloroform anesthesia preponderate over its advantages. It is cardiotoxic, hepatotoxic, and the mortality statistics with chloroform indicate a much greater risk under chloroform anesthesia than under ether or other agents.

On the other hand, one cannot overlook the fact that chloroform has been administered millions of times presumably satisfactorily without the modern equipment of anesthesia. Its induction is prompt, the open drop method is applicable, the vapors are not flammable, and the syndrome is not too unpleasant to the patient. Nevertheless, the principal concern of the anesthesiologist is the life of the patient. To this chloroform presents hazards which are subtle and numerous.

### Cyclopropane, U.S.P.



Cyclopropane is a colorless gas with a characteristic odor, resembling that of petroleum benzin: its m.p. is −126.6°C. and the b.p. is −34.4°C. It is insoluble in water but freely soluble and alcohol and ether. Cyclopropane is very flammable, and its mixtures with air or oxygen are explosive when brought in contact with any source of fire. The gas used for anesthetic purposes must contain not less than 99 per cent (by volume) of cyclopropane. The quantities of unsaturated hydrocarbons permitted to be present are limited by an appropriate potassium permanganate reduction test.

As an anesthetic, cyclopropane is more potent than nitrous oxide and hence permits the admixture during anesthesia of a larger percentage of oxygen. Relaxation of abdominal musculature is quite good during cyclopropane anesthesia. The gas has become established as an important and dependable anesthetic.

**Anesthesia under cyclopropane.** Cyclopropane is used only by inhalation with the closed circuit technic. The induction period is rapid, requiring only 2 to 3 minutes. Induction is quickly accomplished using 15 to 25 per cent of the gas mixed with oxygen in the inspired air. Anesthesia may be maintained by 10 to 15 per cent. The blood concentration during anesthesia is between 17 and 28 mg. per cent.

The potency of the gas permits the patient to be well oxygenated during anesthesia. The recovery from cyclopropane anesthesia is prompt.

Abdominal relaxation is good, but not so satisfactory as that produced by ether or chloroform.

Cyclopropane is not irritating to the mucous membranes except in very high concentrations. Induction is therefore not too unpleasant for the patient unless the concentration is too high. Then laryngeal spasm may occur.

**The respiration under cyclopropane anesthesia.** Cyclopropane does not reflexly stimulate the respiration as does ether. The alveolar membranes are not irritated, and the bronchial musculature is not relaxed. Respiratory movements are not depressed until the anesthesia is quite deep.

**The circulation under cyclopropane anesthesia.** Cyclopropane is not a myocardial poison as is chloroform. It does, however, affect the cardiac rhythmicity. The heart rate is decreased. The blood pressure remains quite normal, and the arterial-venous oxygen difference is decreased. Etsten and Li (1954) demonstrated that the cardiac output under cyclopropane varied with the depth of anesthesia. In the lighter planes (blood-cyclopropane levels 5 to 10 mg. per cent) the cardiac output was reduced about 22 per cent. In the deeper levels of anesthesia the cardiac index returned toward the normal value. They are of the opinion that the increase in $pCO_2$ during the deeper planes of anesthesia was responsible, in part at least, for the increase in cardiac output values. Arrhythmias are common; vagal escape, a-v block, and ventricular tachycardia may occur at any time but more likely when the anesthesia is deep.

Meek *et al.* (1937) showed that cardiac arrhythmias frequently occurred in the dog's heart under cyclopropane anesthesia when the automatic tissue of the heart is sensitized by intravenous injections of epinephrine. In their control dogs the same doses of epinephrine produced only escape phenomena, but under cyclopropane anesthesia, multifocal ventricular tachycardia occurred in nearly all experiments. With this as a basis, Orth *et al.* (1939) stated that epinephrine was interdicted in cyclopropane anesthesia. Using similar sympathomimetic amines, it was observed that this effect was specific for compounds of the series, which like epinephrine contained the catechol nucleus; those containing the phenyl or phenol nucleus did not elicit the response.

Stutzman *et al.* (1942) produced evidence to show that cyclopropane sensitizes the heart of the dog reflexly to epinephrine. The receptors are distributed mainly throughout the peripheral 3 cm. of the mesentery. Nerve impulses pass by visceral afferent fibers through the celiac and superior mesenteric plexuses, splanchnics, and spinal cord to a brain center above the pons. The efferent impulses then reach the heart by way of the cardiac sympathetics, and thus, the irritability of the myocardium is increased.

Price *et al.* (1963) perfused only the head of dogs with blood containing cyclopropane. The agent evoked an increase in systemic arterial mean and pulse pressures and catecholamine concentrations. Exposure of the body alone to cyclopropane elicited diametrically opposite effects. Brain sections involving any part of the medulla obliterated the effects of cyclopropane evoked by head perfusion. They concluded that the effect produced by cyclopropane by head perfusion was caused by selectively depressing "depressor" neurones in the medulla. The "pressor" neurones were apparently affected to a lesser degree. The finer pharmacologic profile of the effect of cyclopropane on the circulation still remains obscure.

Extensive investigation of the conditions affecting the cyclopropane-epinephrine arrhythmias have been conducted. Protection against the syndrome appears to be afforded by increasing the threshold for ventricular fibrillation. Siebens *et al.* (1953) showed that previous injections of epinephrine will increase the threshold for varying periods of time. White *et al.* (1955) observed that diphenylhydantoin sodium in sufficient dosage would afford protection. Of special interest is the fact that these studies revealed that the intravenous injection of glucose enhanced the severity and duration of the arrhythmias.

Virtue and Simmons (1955) found that the cyclopropane-epinephrine arrhythmias were more numerous and longer in duration in dogs during alkalosis. Greisheimer *et al.* (1954) studied the oxygen and carbon dioxide content of the blood of dogs during the induced arrhythmias. They concluded that the phenomenon could not be attributed to an increase of carbon dioxide in the blood or to hypoxia. In 13 of 18 experiments they were able to prevent the arrhythmias by the administration of ether.

Lurie *et al.* (1958) observed that in a series of 31 patients anesthetized with cyclopropane, cardiac arrhythmias seldom occurred provided the $pCO_2$ was normal and the arterial blood concentration of cyclopropane was less than 19 mg. per cent. The incidence of arrhythmias markedly increased with either higher blood levels of cyclopropane or hypercarbia. Some subjects experienced arrhythmias during a rapid return of an elevated $pCO_2$ toward normal. These investigators suggest that the sympathetic nervous system is involved in the origin of the arrhythmias.

Of special significance are the observations of O'Brien *et al.* (1954). Epinephrine injections elicit a prompt rise in arterial potassium level. This potassium increase is prevented by eliminating the hepatic circulation. By hepatectomy in dogs they prevented the rise in arterial potassium. In these dogs the exclusion of blood flow from the liver afforded protection against the cyclopropane-epinephrine arrhythmias in 17 out of 18 animals. This is strong suggestive evidence that the cardiac sensitization in some manner is associated with the arterial potassium rise produced by the injection of epinephrine.

DiPalma (1956) demonstrated that acetylcholine would block the ventricular arrhythmias evoked by hydrocarbons and epinephrine. He is of the opinion that acetylcholine plays an important role in this syndrome. DiPalma offers the explanation that sensitization of the heart to epinephrine involves the inhibition of its "natural antagonist" acetylcholine by the hydrocarbons. It is of interest that the action of acetylcholine in these studies was not blocked by atropine.

Most other common hydrocarbons, including gasoline, also produce sensitization upon inhalation (Chenoweth, 1946). The authors studied a large series of cyclic and noncyclic hydrocarbons and found that all of them produced cardiac sensitization to epinephrine in the dog. Ethylene alone was unique in this respect. It did not produce sensitization of the heart in either the dog or cat.

Procaine and procainamide are used intravenously to reduce the sensitivity of the automatic tissue of the heart under cyclopropane anesthesia clinically. Many other pharmacologic agents are also effective in preventing the cardiac arrhythmias induced by cyclopropane. For example, Wenbury *et al.* (1957) observed that certain of the phenothiazine derivatives provided adequate protection. Perphenazine was found to be the most effective.

The action of epinephrine just after injection of 0.01 mg./kg. upon the heart of the monkey is shown in figure 22-2.

This sensitization of cardiac automaticity is one of the dangers in the use of cyclopropane. Excitation with the release of endogenous epinephrine predisposes the heart to arrhythmias just as does the injection of the hormone.

Occasionally, after cyclopropane anesthesia, a fall in blood pressure occurs. The clinical syndrome is called "cyclopropane shock." Dripps (1947) presented evidence to show that cyclopropane anesthesia may produce a severe respiratory acidosis. Buckley *et al.* (1953) investigated the mechanism of the shock syndrome further. They made mass spectrometric analyses of the carbon dioxide tensions of patients under cyclopropane anesthesia and correlated these data with the blood pressure effects. When patients were allowed to breathe unassisted, alveolar carbon dioxide accumulated, and the blood pressure rose. At the cessation of anesthesia frequently an abrupt fall in blood pressure occurred. Thus, it appears that the proper prophylaxis to prevent this syndrome may be achieved by the maintenance of normal alveolar carbon dioxide tension by manually augmented respiration of the patient.

**Visceral changes under cyclopropane.** Anesthesia with cyclopropane is not known to affect significantly either the liver or the kidneys. Functional tests remain normal for both organs. There are no unusual pathologic findings in the urine attributable to cyclopropane. Other tissues are not injured.

The bleeding time remains unchanged, and the clotting time of blood is not significantly affected by cyclopropane anesthesia.

Henneman and Bunker (1961) studied venous and arterial blood levels of glucose, pyruvate, lactate, citrate, α-ketoglutarate, total ketones, and serum inorganic phosphorus under cyclopropane, ether, and thiopental anesthesia in man. Certain patients were fasted and others were given glucose. The changes for the most part were not significant under anesthesia with any of the agents. They suggest that such alterations as occurred were comparable to the effects elicited by the administration of epinephrine or norepinephrine to unanesthetized individuals. There were elevations in serum inorganic phosphorus that are suggested as being sequential to a depression of renal phosphate excretion. Glucose tolerance was depressed by each anesthetic; this they attribute to a possible inhibition in glucose transport or the phosphorylating mechanism.

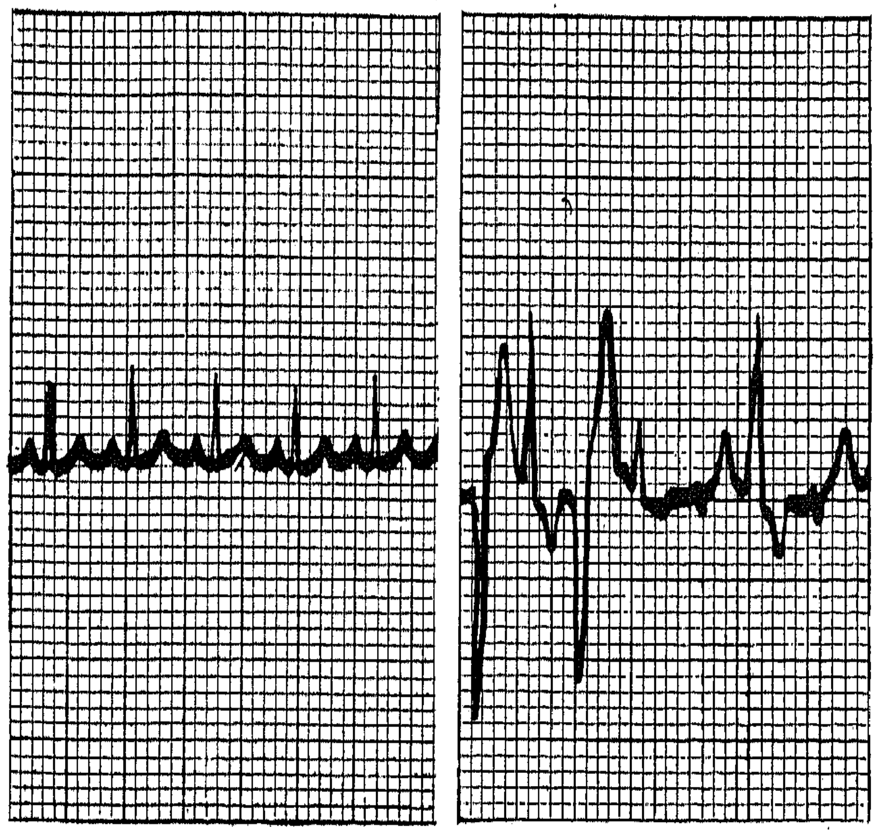


FIG. 22-2. Electrocardiogram Lead II. Monkey; left under cyclopropane anesthesia; right upon the injection of epinephrine.

**Advantages and disadvantages of cyclopropane.** The advantages of cyclopropane as an anesthetic exceed its disadvantages. In many respects cyclopropane closely approaches the ideal anesthetic agent.

The disadvantages of cyclopropane are mainly 3 in number. The gas does not provide the profound degrees of abdominal relaxation which are afforded by ether. The sensitization of the automatic tissue of the heart to epinephrine and certain other sympathomimetic amines is a distinct danger. The explosiveness of mixtures of cyclopropane and oxygen has been the cause of many serious anesthetic accidents.

On the other hand, cyclopropane provides an ease of induction that is lacking with ether. The gas is not very irritating to the respiratory membranes. It produces no visceral damage. The patient awakens rapidly from cyclopropane anesthesia, and the incidence of nausea and vomiting is definitely less frequent than that which occurs after ether anesthesia.

**Ethylene, N.F.** $CH_2{=}CH_2$. Ethylene is a colorless gas, slightly lighter than air. It has a mild sweet odor and taste. One volume of ethylene dissolves in 4 volumes of water at 0°C. and in about 9 volumes of water at 25°C. It is readily soluble in oils and alcohol.

**Anesthesia under ethylene.** Ethylene is not unpleasant to inhale. Its vapors are not irritating to the respiratory membranes. Induction can be accomplished only by high concentrations of the gas, 80 to 90 per cent. These produce a mild hypoxia, but the first plane of surgical anesthesia can be maintained with safety.

During surgical anesthesia approximately 140 mg. per cent must be maintained in the blood. The gas is unaffected by tissue metabolism. It leaves the body promptly and unchanged. Some of the gas diffuses through the skin.

The relaxation produced by ethylene is not sufficient for satisfactory abdominal surgery.

**General anesthetic effects of ethylene.** Ethylene anesthesia has little effect upon respiration, circulation, liver, kidneys, or other systems or organs of the body. The principal drawbacks which prevent its widespread use are: (1) insufficient relaxation; (2) concentrations sufficiently high to produce hypoxia must be employed; and (3) mixtures of this unsaturated hydrocarbon and oxygen are very explosive. Many tragic accidents have been caused by the ignition of ethylene-oxygen mixtures by static electric sparks.

**Ethyl Chloride, N.F.** $C_2H_5Cl$. At low temperature or under increased pressure, ethyl chloride is a colorless, mobile, and very volatile liquid. It boils between 12 and 13°C. Its specific gravity is 0.921 at 0°C. Ethyl chloride has a characteristic ethereal odor and a burning taste. Its vapors burn with a smoky, greenish flame with the production of hydrogen chloride.

**General anesthesia with ethyl chloride.** Ethyl chloride is a powerful, rapidly-acting general anesthetic. Induction can be achieved with ethyl chloride even more rapidly than with chloroform. It is difficult safely to maintain a prolonged anesthesia with ethyl chloride. Therefore, the agent is used principally to induce anesthesia in children, to be followed quickly with ethyl ether after induction occurs. Since the introduction of halothane, this use of ethyl chloride appears to be rapidly decreasing.

Four per cent of ethyl chloride in the air is sufficient to produce anesthesia. Approximately 30 mg. per cent in the blood is sufficient for anesthesia. Its potency, therefore, is comparable to that of chloroform. The lethal blood concentration of ethyl chloride is 40 mg. per cent.

The myocardium is depressed directly by ethyl chloride. Ventricular fibrillation has occurred from its use. The blood pressure falls during anesthesia with ethyl chloride owing to peripheral vasodilatation, cardiac slowing (vagal effect), and direct depressant action on the vasoconstrictor center.

Ethyl chloride enjoys use as a local anesthetic. This is due to its rapid evaporation from the skin. This freezes the tissues and produces insensibility to pain. If the operation is on the face or neck, such as lancing a carbuncle, every precaution should be taken to prevent the inhalation of the gaseous ethyl chloride by the patient. General anesthesia of a dangerous depth may rapidly ensue. Deaths have resulted from failure to observe these precautions.

The unsaturated analog of ethyl chloride, namely, vinyl chloride $CH_2{=}CHCl$, has been recommended for use as an anesthetic agent. Oster and the authors (1947) compared the 2 agents and from experiments on dogs concluded that vinyl chloride was not suitable as a general anesthetic in man.

**Trichloroethylene, U.S.P.** $CCl_2{=}CHCl$. Trichloroethylene (also called trichlorethylene) is a clear, colorless, mobile liquid. It has a characteristic odor which resembles that of chloroform. Trichloroethylene boils between 86 and 88°C. Its specific gravity at 25°C. is about 1.46. Because of the fact that this unsaturated, halogenated hydrocarbon is decomposed by light in the presence of moisture, the Pharmacopeia permits the addition of 20 mg./100 ml. of ammonium carbonate as a preservative. In addition, 0.01 per cent of thymol has been found to be an excellent preservative. Anesthetic trichloroethylene is colored blue so that it will not be mistaken for ether and used in a closed circuit with soda lime. The latter decomposes trichloroethylene. Its vapors are not flammable.

Butler (1949) showed that in the dog a portion of inhaled trichloroethylene was likely converted into chloral hydrate. This substance is then transformed into trichloroethanol and trichloroacetic acid. These products are excreted in the urine.

The anesthetic syndrome with trichloroethylene resembles that of chloroform. It is more difficult to control the patient than with chloroform. Also much excitation has been reported in the induction stages.

Investigations by Hewer (1941) in England, and Sadove (1952) in America, have led to the use of trichloroethylene with nitrous oxide and oxygen as an anesthetic. By means of specially designed vaporizers, a mixture of 75 per cent nitrous oxide and 25 per cent oxygen is made to pass over trichloroethylene. The vaporizer can be so adjusted that 0.2 to 0.8 per cent of trichloroethylene will be carried to the face mask. This provides excellent analgesia and increased relaxation with nitrous oxide anesthesia. Besides, adequate oxygenation is maintained. Under the names *Trimar* and *Trilene* this form of simple, nonflammable and rapid anesthesia enjoys limited use. It is especially recommended for dental extractions, orthopedic manipulations, cystoscopy, and similar short surgical procedures.

**Rare atmospheric gases as anesthetics.** In 1948 the authors experimented with the rare atmospheric gas krypton as an anesthetic agent. It has an oil-water coefficient greater than unity. High concentrations of 50 per cent or more produced only blurred consciousness when inhaled. Cullen *et al.* (1951 *et seq.*) employed the rare gas xenon, with a higher oil-water coefficient, with success as an anesthetic agent in animals. Later they used it in human beings for several surgical procedures. The potency is low, comparable to ethylene. Approximately 80 per cent in the inspired air is required for anesthesia. Using radioactive xenon, Cullen and his associates studied the distribution of the gas in the central nervous system and other organs. Xenon was not found to inhibit a variety of enzyme systems present in brain tissue. Of special interest is the fact that in addition to high concentrations in the central nervous axis, the gas was found to concentrate itself in the adrenal glands. Should this gas become abundant and inexpensive it may prove to be the ideal anesthetic. Indeed, Cullen and his associates have made an excellent contribution to the field of general anesthesia by the exploration of the anesthetic properties of xenon.

**Balanced anesthesia.** The mixing of 2 or more anesthetic agents in order to achieve advantage in administration, degree of relaxation, and safety, dates back to 1848 when John Galb of England suggested mixing ether and chloroform. There has been a recent revival in interest in this field. It is clear that lower concentrations of each agent may be used. Thus, desirable effects can be accentuated and undesirable actions minimized by properly balancing the anesthetic mixture. Shane (1953 *et seq.*), after many trials with different agents, developed a balanced anesthetic mixture containing about 12 per cent cyclopropane, about 30 per cent nitrous oxide, and the remainder oxygen. The patient is rendered unconscious by thiopental or Evipal sodium. The gas mixture is administered by a semiclosed technic, allowing a portion of the exhaled mixture to escape into the room. With this balanced mixture the depth of anesthesia cannot readily go beyond plane 1 of stage III. *d*-Tubocurarine or succinylcholine may be necessary to produce additional relaxation.

It is obvious that this balanced mixture produces a readily controllable degree of anesthesia. The hypoxia of nitrous oxide anesthesia is obviated by the addition of the more potent cyclopropane. By a reduction of the cyclopropane concentration, the frequency of cardiac arrhythmias is reduced. Recovery is generally prompt and uneventful. Postanesthetic sequelae are few. To the authors' knowledge this mixture with the proper ancillary drugs produces a most satisfactory anesthesia for most surgical procedures in patients in various age groups.

**General hypothermia anesthesia.** Walther (1862) immobilized rabbits at 20°C. and found that anesthesia was sufficiently deep for surgery. Simpson and Herring (1905) showed that in deeply anesthetized cats in which shivering did not occur, reflexes disappeared from the brain downward. The only reflex which prevailed at low temperatures until death was the knee-jerk. Hamilton (1937) showed that hypothermia in laboratory animals produced a descending paralysis of the central nervous axis, reversible upon warming. Wetting the skin was found to hasten body cooling. Other investigators from time to time have employed hypothermia to obtund severe pain for short periods.

A surge in interest in hypothermia, sometimes called "artificial hibernation or neuroplegia," occurred from the work of the French investigators with the phenothiazine derivative chlorpromazine (1950 *et seq.*). Using this compound along with other agents, they were able to produce drug-induced hypothermia for anesthetic purposes. Their so-called "Lytic Cocktail" consisted of 50 mg. of phenergan, 50 mg. of chlorpromazine, and 100 mg. of meperidine. Temperature falls of 2 to 3 degrees are produced by the intravenous use of these agents. Further reductions in body temperature with the Lytic Cocktail are difficult to achieve without skin cooling or causing dangerous depression of the circulation. With the administration of the Lytic Cocktail, blood pressure falls and a marked degree of somnolence ensues. Adjunct anesthetics which may be required for surgery, such as thiopental sodium, are markedly reduced in quantity.

In the United States the Lytic Cocktail-induced hypothermia has not been considered as safe as "Generalized Body Hypothermia." With this procedure, involving mainly the chilling of the skin, the Lytic Cocktail drug combination is not considered important to the basic technic. If used at all, a much reduced dosage level is employed. Indeed a volatile anesthetic appears to be the preference because of its ready reversibility of action, and further, the detoxification mechanism of the patient is not required to terminate its activity.

When body temperature is reduced to 30 or 28°C. there is a concomitant reduction in tissue oxygen demand, and respiration diminishes.

The phenomenon of "cold narcosis" under the conditions often employed, namely, general anesthesia plus cold, is likely the result of the anesthetic agent and the hypothermia. Electroencephalographic studies seem to indicate that cerebral activity is not markedly depressed by hypothermia *per se*, but is profoundly affected by small increments of the level of the anesthetic employed (Hackett, 1957).

The hypotension that may be elicited causes a marked reduction in hemorrhage under surgery. Hypotension is usually seen only in temperatures below 28° to 30°C. Above this temperature blood pressure is usually elevated because of constriction of peripheral vessels and increased myocardial efficiency. The hypothermia may be tolerated for several hours without harmful sequelae. The great advantage of hypothermia anesthesia appears to lie in cardiac surgery. With hypothermia the blood flow to the heart may be occluded for time periods sufficiently long to permit intracardiac maneuvers under direct vision.

The principal danger accompanying hypothermia appears to be circulatory failure. This is generally due to ventricular fibrillation. The fibrillatory process stems from a prolongation of the latent period of the cardiac conduction system so that any stimulation, however slight, may result in ventricular fibrillatory twitching. It has been observed from experiments on dogs, that lowered body temperature was the most important factor contributing to fibrillation. For example, in 40 experiments at 27°C., no fibrillation occurred; however, it was frequently encountered in 50 experiments at 20°C. Zeavin, Virtue and Swan (1954) found electric defibrillation ineffective. On the other hand, they achieved success by the injection of potassium chloride solution into the coronary arteries. Others hold the view that the hypothermic fibrillating heart will readily respond to electrical defibrillation providing sufficient voltage and amperage are applied (Hackett, 1957).

Virtue (1954) induced sleep with thiopental sodium prior to the chilling of the body in the ice bath. Cyclopropane was employed to diminish reflexes to a point where ether could be added without stimulation. Emphasis is placed on the fact that temperature may continue to drop after the patient is taken from the bath. This may be checked by the circulation of warm water through a rubber mattress on the table.

The limits of hypothermia with surface cooling technic have been variously set at 25° to 28°C. Work involving temperatures down to 6° to 10°C. has been dependent on the use of blood stream cooling utilizing extracorporeal pumps and a heat exchanger. The pump, by supporting the flagging myocardium, eliminates the primary complication of deep hypothermia.

It has become apparent that hypothermia is being used mostly as an adjunct in heart surgery and neurosurgery. Recently hypothermia has been employed in the treatment of septic shock which has failed to respond to vasopressor and corticoid therapy.

For the many details of hypothermic procedures and the physiologic changes occurring during artificial hibernation, the reader is referred to the voluminous literature on this subject in physiology and anesthesiology.

### Fluorinated Volatile Anesthetics

The introduction of fluorine atoms into the molecules of lower molecular weight hydrocarbons or ethers exerts a marked influence upon their physical and pharmacologic properties. To illustrate, perfluorodiethyl ether is a nonflammable and inert chemical compound. It appears that, although the introduction of chlorine or bromine atoms into these molecules enhances their anesthetic potency, fluorine atoms generally serve to diminish anesthetic activity. However, sufficient fluorination will abolish flammability. The first fluorinated ether used on man as an anesthetic was trifluoroethyl vinyl ether (Fluoromar). It was the outcome of a study on fluorinated hydrocarbons and ethers conducted by the authors in 1953. Its clinical usefulness was determined by Sadove, Dornette, and others. Fluoromar is now available as a volatile anesthetic. It is of interest to note that hexafluorodiethyl ether (Indoklon) studied by Krantz *et al.* (1957) is a convulsive agent and is used for convulsive therapy in mental illness.

**Trifluoroethyl Vinyl Ether (Fluoromar, Fluroxene)** $CF_3 \cdot CH_2{-}O{-}CH{=}CH_2$, b.p. 43.2°C., sp. gr. 1.13. Fluoromar is a clear, colorless liquid emitting a mild, unobjectionable odor. The organically bound fluorine is stable in the body and not altered by contact with soda lime.

The pharmacologic properties of Fluoromar were studied by Krantz *et al.* (1953). The early clinical use of Fluoromar was explored by Sadove *et al.* (1956) and Dornett (1956). The agent evokes rapid induction of anesthesia at comparatively low levels in the inspired air. Relaxation of the musculature is good, and the anesthetic syndrome is characterized by a marked analgesia that extends beyond the return to consciousness. Fluoromar appears to be especially advantageous for open chest surgery. Although Fluoromar is flammable, its lower limit of flammability is 4.2 per cent and it is not readily ignited.

**Pharmacologic studies with Fluoromar.** Fluoromar was shown to be somewhat more potent than ether. Its anesthetic index is comparable to that of ether. The blood pressure is slightly lowered in the surgical planes of anesthesia. No arrhythmias were encountered in dogs and monkeys. The EKG showed only a flattening of the T-wave. As the blood pressure is lowered by deepening the anesthesia, a tachycardia was observed. The heart was not sensitized to challenging doses of epinephrine under Fluoromar anesthesia. The EEG pattern in monkeys with Fluoromar resembled the pattern under ether anesthesia. Fluoromar produced no change in blood urea nitrogen, sugar, carbon dioxide-combining power, hemoglobin, red count, white count, or clotting time. Histologic studies performed on the 5th postanesthetic day showed no change in sections of canine liver and kidney. Similar histologic studies done in dogs anesthetized 3 hours each week for 3 weeks, as well as one hour each week for 8 weeks, showed no change in the liver, heart, lungs, or kidneys. Delayed toxicity studies on rats also showed no adverse effect on liver or kidneys.

**Clinical studies with Fluoromar.** The clinical studies (Dornette 1963) with Fluoromar have revealed that it is a stable compound with a boiling point and vapor pressure within the intermediate range, allowing simplicity of vaporization and administration. Induction is rapid and as a rule pleasant and free of appreciable excitement. This feature is especially helpful in pediatric cases. Rapid change of planes of anesthesia is possible with Fluoromar. The absence of irritating qualities with this agent produce minimal salivation and laryngospasm. Bronchospasm has not been reported with Fluoromar anesthesia.

There is absence of cardiovascular depression in lighter planes of anesthesia. The depression that may occur in deeper planes of anesthesia is rapidly reversible when the level of Fluoromar anesthesia is lightened. In deep levels the decreased blood pressure is due to decreased peripheral resistance rather than to reduction of cardiac output. Pulse is regular, with some tendency toward bradycardia in deeper planes of anesthesia. Under Fluoromar anesthesia there is stability of cardiac rhythm. Nodal rhythm is the only significant change reported. Fluoromar does not sensitize the myocardium to epinephrine.

Recovery is rapid with early return of reflexes. Postoperatively, there is minimal nausea, emesis, and excitement, with no effect on the hepatic or renal system.

Fluoromar is compatible with all other anesthetic agents, intravenous muscle relaxants, vasopressors, oxytocics, and soda lime. It is adaptable for use with all technics of inhalation anesthesia. Fluoromar may be employed singly or in combination with any of the other general anesthetic agents.

**Advantages of Fluoromar anesthesia.** Fluoromar is useful in producing good obstetrical analgesia. It is excellent for pediatric anesthesia because it produces a smooth, pleasant induction and sufficient relaxation without additional muscle relaxants. This agent is excellent in cardiovascular surgery because it produces minimal cardiovascular depression and allows rapid change in anesthetic levels. Fluoromar is a good anesthetic for poor risk patients since in light levels of anesthesia there is an absence of cardiovascular and respiratory depression, and it is not hepatotoxic.

**Halothane (Fluothane).** Raventos (1956) introduced the mixed halogenated hydrocarbon 1,1,1,trifluoro-2,2-bromochloroethane as an anesthetic agent. The use of halothane as a clinical anesthetic agent was accepted with rapidity in England, Canada, and the United States.

**Physical properties of halothane.** Halothane is a clear, colorless mobile liquid with a characteristic odor which resembles that of chloroform. The liquid boils at 50.2°C. and has a sp. gr. of 1.86 at 15°C. Its vapors are completely nonflammable. The oil-water coefficient is 330 which is indicative of its powerful anesthetic activity.

**Pharmacologic properties of halothane.** Raventos (1956) showed that halothane vapor when inhaled caused rapid and deep anesthesia in a variety of laboratory animals. The agent enters and leaves the body unchanged. Its principal pharmacologic action, aside from anesthesia, was hypotension. The degree of hypotension appears to be a function of the depth of anesthesia. Anesthesia with halothane did not evoke cardiac arrhythmias, but the myocardium was sensitized to challenging doses of epinephrine. The only pathologic lesion noted by Raventos following anesthesia with halothane was mild dilation of the proximal tubules of the kidney. There was no impairment of renal function. Krantz *et al.* (1958) observed a mean decrease of 47 per cent in the oxygen uptake of the monkey under halothane anesthesia. This is comparable to chloroform anesthesia. The oxygen uptake of rats' hearts ventricular slices *in vitro* also exhibited diminished oxygen uptake when exposed to anesthetic concentrations of halothane.

Stephen *et al.* (1958) conducted extensive studies on laboratory animals with halothane and made comparisons with nonfluorinated anesthetics. They found halothane to be compatible with many of the ancillary drugs used in anesthesia such as atropine, methoxamine, and ephedrine. They observed cardiac arrhythmias induced by challenging doses of epinephrine and norepinephrine. It appears that mixed halogenated hydrocarbons containing fluorine evoke sensitization, but this does not prevail to any appreciable degree with ethers.

Of special interest is the compatibility of halothane with succinylcholine chloride. They observed no unusual response to this muscle relaxant under halothane anesthesia in dogs. No alterations in blood pressure were noted during the period of effective relaxation.

Because halogenated hydrocarbons are notorious for their hepatotoxic action, these same investigators carried out studies on dogs and monkeys by anesthetizing them for 3 hours a day on 5 consecutive days. Hepatotoxicity was most marked with chloroform, minimal with halothane, and negligible with ether.

The study on laboratory animals by Stephen *et al.* (1958) is of special significance when considered in the light of the blind technic study conducted by Bamforth *et al.* (1960). A series of 100 patients were anesthetized with halothane or chloroform supplemental to nitrous oxide-oxygen anesthesia. The anesthesiologist was not informed as to the agent he employed. His only criterion was his observation of the anesthetic syndrome. Their conclusion was that the changes in blood pressure, pulse rate, respiration, and complications during anesthesia were similar in the two groups of patients. They state, "We believe that halothane bears a strong clinical resemblance to chloroform."

This last statement is also shared by the authors. This is especially true with regard to ease of induction, hypotensive effect, and sensitization of the myocardium to epinephrine. On the other hand, from experiments in animals and human anesthesias, it is clear that of the 2 agents, halothane evokes a lesser degree of hepatotoxicity.

**Halothane and the liver.** Like most halogenated hydrocarbons, halothane must be considered as potentially hepatotoxic, but in considering more than 10 million anesthesias with with this agent, hepatotoxicity was seldom encountered (Bunker, 1962).

Jones *et al.* (1958) evaluated the relative hepatotoxicity of several inhalation anesthetics and observed that chloroform was the most toxic and ethyl ether the least toxic. Halothane produced liver cell injury which was manifested as a fatty infiltration without necrosis. Virtue and Payne (1958) observed a postoperative death caused by halothane anesthesia. No effect was seen on the liver histopathology of dogs exposed to halothane for 3 hours while adequately ventilated. Also, no adverse effects were noted when this agent was administered in an atmosphere slightly deficient in oxygen (Haley and Wyant, 1959). Greene *et al.* (1959) investigated the effects of 2 doses (dose for analgesia and for surgical anesthesia) on the liver of dogs with halothane, chloroform, and diethyl ether. Chloroform in each concentration produced structural and functional hepatic changes which were more severe than those observed with halothane and ethyl ether. Most dogs returned to normal within 9 days. Brody and Sweet (1963) noted in their report that 3 out of 4 cases under study with halothane anesthesia died of massive hepatic necrosis. In a recent review on halothane and hepatic necrosis, Vandam (1963) indicated that the relationship between halothane and liver changes has by no means been proved; further controlled studies are needed to solve conclusively this serious problem. A total of 12 hepatic deaths (mostly in cholecystectomies) has been reported in the literature incriminating halothane as the causative agent. At present, halothane is not recommended for use in patients with known liver or biliary tract disease or for obstetrical use. Morris (1963) reported, "Severe liver damage was demonstrated in patients receiving carbon dioxide during halothane and methoxyflurane anesthesia. No damage was seen in association with Fluoromar and nitrous oxide anesthesia. The damage seen was similar to that observed after chloroform administration. Among the significant results of this study is the lack of liver damage following Fluoromar, indicating that it is the only halogenated drug not capable of producing hepatic damage."

**Halothane and the circulation.** The cause of the hypotensive action of halothane has been the subject of extensive investigation. This effect is shared by chloroform, but it is not marked with the fluorinated ethers. Wyant *et al.* (1960) hold the view that the hypotension is due to peripheral vasodilatation; however, their work does not indicate the mechanism of the hypotension. It appears that the hypotension involves several components. The first of these is decreased cardiac output. This results from direct myocardial depression. The second facet is decreased peripheral resistance evoked by a depressant action on the vasomotor center and a relaxant action on the walls of the blood vessels. The third factor is a selective autonomic ganglionic blockade as suggested by Raventos (1956). Burn *et al.* (1957) were unable to demonstrate any strong ganglionic blocking action produced by halothane. If autonomic ganglionic blockade is a factor in the hypotension of the anesthetic syndrome of halothane, it appears to be of minor significance.

Johnstone (1956) demonstrated that halothane evokes a direct action on the conduction system of the heart. He showed that this was cholinergic in character and could be adequately blocked by atropine. Bradycardia is often observed during halothane anesthesia, frequently this is masked by atropine premedication. Dundee and Black (1960) suggest that the changes in the heart rate may be either due to vagal stimulation or depression of sympathoadrenal activity.

Virtue *et al.* (1962) conducted an interesting comparison of the respiratory and hemodynamic effects of halothane and Fluoromar anesthesia on 10 normal subjects. Their data confirm many of the observations that have been recorded by various investigators.

They observed that under anesthesia with halothane the oxygen uptake is depressed significantly. This does not prevail with Fluoromar. The same type of diminution of oxygen uptake under halothane anesthesia was shown by Krantz *et al.* (1958) using monkeys.

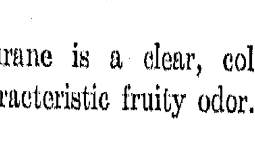
It appears that no consistent changes in cardiac output occurred under anesthesia with either agent. Halothane anesthesia is accompanied by a significant degree of hypotension that does not prevail with Fluoromar. The authors commented favorably on the rapidity of the awakening of the subjects from Fluoromar anesthesia.

**Clinical use of halothane.** Using concentrations in the inspired air of 2 to 2.5 per cent (which must be meticulously controlled by an especially designed vaporizer) smooth, easy, and rapid induction may be achieved. Surgical anesthesia may be produced within 5 to 7 minutes.

Dobkin (1959) reported on 90 patients receiving halothane for major surgical procedures. They found halothane to provide satisfactory anesthesia. Data derived from arterial blood samples showed no evidence of distorted acid-base balance even after prolonged anesthesia.

Abajian *et al.* (1959) used halothane in 5000 cases. They reported no evidence of hepatic, renal, or "undue" myocardial toxicity. They concur in the previous statements of ease of induction. Relaxation appears to be good under halothane anesthesia, and skeletal muscle relaxants do not appear to be necessary. Numerous other reports in the literature confirm the value of halothane as an anesthetic agent and support the observations of the foregoing investigators (Moyers and Pittinger 1959).

**Methoxyflurane (Penthrane)** was introduced into anesthesia through the studies of Van Poznak and Artusio (1960). Methoxyflurane is 2,2-dichloro-1,1-difluoroethyl methyl ether as shown in the formula:



$$\begin{array}{c} \phantom{H-{}}\mathrm{Cl}\ \ \mathrm{F} \\ \phantom{H-{}}|\ \ \ \ | \\ \mathrm{H{-}C{-}C{-}O{-}CH_3} \\ \phantom{H-{}}|\ \ \ \ | \\ \phantom{H-{}}\mathrm{Cl}\ \ \mathrm{F} \end{array}$$

Methoxyflurane is a clear, colorless liquid having a characteristic fruity odor. The boiling point is 104.65°C. and the sp. gr. is 1.42 at 25°C. Methoxyflurane is completely stable in the presence of alkali, air, light, or moisture and can be safely employed in a closed circuit.

The concentration of methoxyflurane in anesthetic mixtures is limited to a maximum of about 4 per cent at 23°C. by the vapor pressure of methoxyflurane and by the efficiency of the vaporizer.

Chenoweth (1962 *et seq.*) studied extensively the pharmacologic responses to methoxyflurane. In dogs anesthesia was induced in 10 minutes and muscular relaxation was excellent. The emergence time from anesthesias of 30 to 150 minutes was 60 to 120 minutes. Induction was slow, but anesthesia could rapidly be induced with thiopental sodium or halothane and then supplemented with methoxyflurane.

Electroencephalographic studies on humans as well as dogs demonstrate in light levels of anesthesia fast, regular, low-voltage activity, and as anesthesia is deepened there is a slight shift of the spectrum to slower frequencies and slightly greater amplitude. This change is a subtle one, however, and is not nearly as marked as the change seen with diethyl ether, cyclopropane, or thiopental.

Although the respiratory response to methoxyflurane is somewhat similar to that of ether, there was no indication of respiratory stimulation as is observed with ether. Minute volume was slightly increased during light anesthesia, but depressed during deep anesthesia.

The blood pressure is lowered by anesthesia with methoxyflurane. The depressor response is progressive with the depth of anesthesia. The mechanism of the depressor response has not been delineated. Since atropine was found to diminish the depressor response, it appears that vagal stimulation is one of its components. The pulse rate is generally decreased under methoxyflurane anesthesia. Ventricular arrhythmias were not encountered; neither were they induced by challenging doses of epinephrine. Generally, the halogenated ethers do not sensitize the heart to epinephrine in contradistinction to the halogenated hydrocarbons which do so invariably.

There was no evidence of damage to the elements of blood and no change in the coagulation time by methoxyflurane anesthesia.

Methoxyflurane appears to have about the same effect upon liver function as does ether. Of all the various tests for liver function, the Bromsulphalein test appeared to be the most sensitive in these studies. Methoxyflurane is a potent volatile anesthetic as first suggested by Van Poznak and Artusio (1960). It has been widely used, and these authors' work amply confirmed. It appears that slow induction, slow emergence, and hypotension during anesthesia are its principal drawbacks.

**Other fluorinated anesthetics.** Investigations in the field of fluorinated anesthetic agents have received a great stimulus from the success of halothane and Fluoromar and the greater availability of fluorinated hydrocarbons and ethers. Many derivatives of propane such as 3-chloro-1,1,2,2-tetrafluoropropane and its brominated analog have been studied (Fabian *et al.* 1960). As more compounds become available, the criteria for the ideal anesthetic agent become more stringent. It does appear that use of fluorinated anesthetics has removed the fire hazard from anesthesia and increased the spectrum of new compounds from which one might seek the ideal anesthetic.

## THE NONVOLATILE ANESTHETICS

Tribromoethanol (Avertin) and thiopental sodium (Pentothal) are representatives of the class of nonvolatile anesthetics. The former is administered rectally and the latter is given mainly intravenously. Volatile anesthetic agents are more readily controlled than the nonvolatile substances. The nonvolatile anesthetic agents in case of threatened collapse cannot be removed rapidly from the circulation. One is dependent upon detoxification by the tissues or excretion by the kidneys and the administration of antagonistic drugs. With the volatile anesthetic agents, the removal of the mask from the patient's face immediately initiates the rapid exodus of the anesthetic agent from the patient's blood. This affords a degree of safety that cannot be achieved with a nonvolatile anesthetic. It is a safety valve in the anesthetic procedure which cannot be overestimated.

**Tribromoethanol Solution, U.S.P.** $CBr_3 \cdot CH_2OH$. Tribromoethanol solution is a solution of tribromoethanol in amylene hydrate. Each 100 ml. contains 100 gm. of the brominated ethanol. The solution is called *Avertin* or *Avertin Fluid.*

Tribromoethanol was introduced as an anesthetic agent in 1926. Under the aliphatic alcohols it was observed that as the molecular weight of the alcohols increased, their narcotic activity increased also. With alcohols of exceptionally high molecular weight, however, the solubility in water is so low that they do not elicit narcotic action.

In tribromoethanol 3 hydrogen atoms of ethanol with a combined atomic weight of approximately 3 have been replaced by 3 bromine atoms with a total atomic weight of about 240. Thus, the molecule may be considered as a primary, aliphatic alcohol of high molecular weight. The introduction of these bromine atoms into the molecule confers a high oil/water coefficient on the compound. To enhance its miscibility with water it is dissolved in amylene hydrate $(CH_3)_2C_2H_5 \cdot C \cdot OH$. Amylene hydrate itself exhibits anesthetic activity in addition to the conferring of solubility. Hence, the action of tribromoethanol is the dual action of the 2 compounds tribromoethanol and amylene hydrate. For a detailed description of anesthesia with tribromoethanol see page 497 5th edition of this text.

**Thiopental Sodium, U.S.P. (Pentothal Sodium).** Thiopental is one of the most widely used anesthetic agents. It is administered intravenously and to some extent rectally. It is a nonvolatile or fixed anesthetic.

Intravenous anesthesia is not new. Burkhardt (1909) used ether in diluted solutions intravenously. The volatility of ether and low solubility in water presented technical difficulties in its use. Besides, the injections were painful and often produced hemoglobinuria.

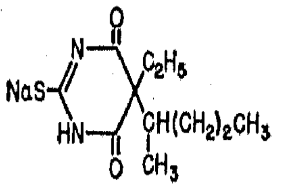
The introduction of amobarbital sodium (page 400) into medicine in 1928 as a hypnotic brought to the attention of the anesthesiologist the possibility of the use of this substance as an intravenous anesthetic. After a very enthusiastic reception and successful use in many clinics the drug was replaced by Evipal sodium (sodium N-methyl-cyclohexenylmethyl barbiturate). Amobarbital produced prolonged sleep after the operation which predisposed the patient to respiratory complications. Besides, as the effect subsided the patient frequently passed through a distressing period of delirium.

Evipal was introduced by Weese and Scharpff (1932). Its action is of short duration, and it stood as the best drug for intravenous anesthesia until 1934. About this time interest was revived in the thiobarbiturates, and thiopental sodium was introduced shortly thereafter.

The thiobarbiturates were studied by Fränkel (1923) who reported that as a class they were more toxic than their oxygen analogues, the barbiturates. Tabern and Volwiler (1935) prepared thiopental, and after an extensive pharmacologic study it was given clinical trial by Lundy and his associates at the Mayo Clinic. Hundreds of papers have appeared on the use of this agent as a general anesthetic. It stands as one of the most important contributions to modern anesthesia.

**Chemical considerations.** Amobarbital, Evipal, and thiopental are barbiturates. The last named is a sulfur-bearing barbiturate or a thiobarbiturate. These substances are related chemically. One observes from the formula, page 400, that the thiobarbiturate differs from the barbiturate in that the oxygen atom of the urea portion of the molecule is replaced by a sulfur atom. The thiobarbiturates are readily detoxified and are consequently short-acting compounds. When used for anesthetic purposes this is a decided advantage. The minimal hypnotic dose of thiopental sodium administered intravenously to a rabbit produced sleep which lasted for 5 minutes. The oxygen analogue of thiopental, namely pentobarbital or Nembutal, under the same conditions produced sleep which continued for 21 minutes.

**Anesthesia under thiopental sodium.** Thiopental sodium is unstable in solution; hence, the substance is made available in the dry state in sealed ampules. It is dissolved in sterile, distilled water just prior to use. The solutions have been employed in concentrations of 1, 2.5, and 5 per cent. The 2.5 per cent appears to be the concentration of choice among most anesthesiologists, although some prefer the lesser volume of the 5 per cent solution. Lundy and Adams (1942) give the following dosage schedule for the injection of thiopental. Two to 5 ml. of solution (2.5 per cent) are injected slowly in ½ to 1



Thiopental Sodium, U.S.P.
Pentothal sodium (sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate)

minute. The induction is almost immediate; the depth of respiration is depressed. The needle is allowed to remain in the vessel to supplement the initial dose of the agent. This is required as the anesthesia becomes lighter. The quantity of thiopental required varies with the type of patient and the nature of the operation.

This anesthetic is not recommended for operations requiring long anesthesia. The use of thiopental as an unsupplemented anesthetic agent should be confined to procedures requiring not longer than 20 minutes. When quantities of 0.5 to 1 gm. of thiopental sodium are administered, at the peak of anesthesia, within 20 to 30 minutes 1.5 to 2 mg. per cent of the compound is found in the blood. It is rapidly detoxified by the body tissues.

Brodie *et al.* (1950) developed a spectrophotometric method for the determination of thiopental in the blood and other tissues. With it they followed the fate of thiopental in man after intravenous injection. They administered 0.4 gm. in a 2.5 per cent solution within 2 minutes. The plasma levels expressed in mg./l. were: 30 in 2 minutes; 7 in 15 minutes, at which time the subject awakened from sleep; and 3 in 90 minutes. The oxidation of thiopental in the body occurs by the conversion of one of the methyl groups in the side chains in the 5,5 position to a carboxyl group. The metabolite was isolated and found to be devoid of anesthetic activity. Thiopental was found to be nearly completely transformed in the body. The rate, however, is slow, not exceeding 15 per cent per hour. The rapid diminution of plasma levels appears to indicate the storage of thiopental in body tissues. It concentrates in lipoid depots. Taylor *et al.* (1952) showed, that while in the blood of rabbits, thiopental was bound by the plasma to the extent of 75 per cent.

The work of Brodie and his associates confirms previous statements in the literature regarding plasma levels of thiopental made by other investigators. Upon the administration of 1 gm. they found a plasma level of 1.5 mg. per cent in about 30 minutes. Although it had been established previously that thiopental was rapidly oxidized by body tissues, the isolation of this carboxylic acid metabolite is a distinct contribution to our knowledge of the fate of this important agent. Furthermore, Cooper and Brodie (1957) observed that thiopental and pentobarbital are oxidized in rabbit liver homogenates. Thiopental yielded mainly the corresponding acid with a carboxyl group on carbon atom "4." The oxidative process occurs in the microsomes of the liver homogenate and requires reduced triphosphopyridine nucleotide (TPNH) and oxygen. The microsomal activity appeared to be incapable of appreciably splitting the malonylurea nucleus.

Thiopental markedly depresses the cerebral cortex, and its effect on the motor areas is so prompt and dependable that thiopental is used to combat convulsions which may occur under the volatile anesthetics ether and divinyl oxide. The respiration is depressed in thiopental anesthesia. When the agent is first injected, the patient may show a transient apnea. In deep thiopental anesthesia the depth of respiration is markedly diminished, the minute volume exchange is reduced, and oxygen consumption is decreased. Horita and Dille (1955) observed that when dogs were anesthetized with thiopental the laryngeal reflex mechanism was depressed. They suggest that this is mediated through the central action of the agent.

Thiopental causes a fall in blood pressure. The heart rate is increased. There is generally no disturbance in the cardiac rhythm provided the patient is adequately oxygenated. Pollock *et al.* (1955) found no statistical difference in cardiac output between untreated patients and those induced into anesthesia with thiopental and a nitrous oxide-oxygen mixture. When thiopental is administered in shock the blood pressure falls further, respiration is markedly depressed, and marked cardiac dilation occurs.

There are no significant pathologic findings that occur in the liver, kidneys, or other viscera after thiopental anesthesia. Bachman (1955) observed that anesthesia in dogs with thiopental elicited no antidiuretic effect. Under the same experimental conditions ether, cyclopropane, and morphine exhibited some degree of antidiuretic activity. When rats are partially hepatectomized, the anesthesia produced by thiopental sodium is not prolonged. This indicates that the body is not solely dependent upon the liver for the detoxification of this thiobarbiturate. With pentobarbital, however, anesthesia is greatly prolonged by partial hepatectomy.

Abdominal musculature is not sufficiently relaxed for major surgical procedures under a safe concentration of thiopental. Muscle tremors are frequently present. Kraatz *et al.* (1953) demonstrated that pentobarbital and thiopental caused a potentiation of the maximal twitch of the dog and cat tibial muscle. Of the 2, thiopental was the more potent and in low levels was found to antagonize the head-drop of the rabbit produced by curare. These observations appear to substantiate the clinical findings with regard to skeletal muscle tone under thiopental anesthesia.

Beecher and McCarrell (1943) showed that thiopental anesthesia reduced the tissue salt and protein loss in skin and mesentery burns. The losses were significantly less than normal.

For major surgical procedures thiopental anesthesia is supplemented by cyclopropane or nitrous oxide. Further, better relaxation may be obtained by the use of muscle relaxants with thiopental.

Thiopental sodium is also administered rectally as a basal anesthetic and for short procedures. It is given on the basis of 1 gm. for each 50 pounds of body weight of the patient in a 10 per cent solution.

*Clinical use of thiopental sodium.* The surgical procedures for which thiopental sodium appears to be well suited are:

1. Orthopedic operations and manipulations
2. Genito-urinary procedures—cystoscopies and transurethral resections
3. Obstetric repair procedures
4. Dilation and curettage

Thiopental sodium is used as a basal anesthetic in many procedures of surgery. It is also used to produce muscular relaxation in the shock treatment of mentally depressed patients.

Thiopental sodium anesthesia is contraindicated in:

1. Patients who have potential respiratory block or depressed respiration.
2. Thiopental sodium is not recommended for children under the age of 10 years.
3. The agent is not suitable for patients with advanced myocardial disease.
4. It is not suited in cases where the oxygen intake is limited or the distribution of the anesthetic through the tissues may be impaired.
5. Thiopental is not recommended in impending shock or when hemorrhage has occurred.

The antidotes for thiopental sodium are discussed on page 483.

**Thiobarbitone Sodium (Kemithal).** The English investigators Carrington and Raventos (1946) employed another drug for intravenous anesthesia which appears to be competitive with thiopental sodium. The drug is called "Kemithal." It is 5-$\Delta^2$-cyclohexenyl-5-allyl thiobarbituric acid. For a discussion of this drug that enjoys only a limited use at this time see page 503, 5th edition.

**Thiamylal Sodium, U.S.P. (Surital Sodium)** is sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate. This substance may therefore be looked upon as thiosecobarbital sodium. Surital sodium is provided as a mixture with sodium carbonate. The mixture when dissolved in water is adjusted to a pH of about 10.8.

Surital sodium is an ultra short-acting thiobarbiturate and is used for intravenous anesthesia for surgical procedures of short duration. Its anesthetic potency appears to be comparable to that of thiopental sodium.

The action of Surital sodium is rapid, occurring within 20 to 60 seconds, and recovery may be expected within 10 to 30 minutes after the last injection. Surital sodium is detoxified by the liver and therefore is contraindicated with patients with hepatic disease. It should be used with caution in cases of hypoxia resulting from any cause.

Tovell *et al.* (1955) studied by the blindfold technic thiopental and Surital in more than 2000 patients. They concluded that in human anesthesia there was no statistically significant difference between the anesthesia produced by the 2 agents as far as potency, cardiotoxicity, respiratory depression, incidence of laryngospasm, and recovery time are concerned. Greater duration of laryngospasm was observed with Surital. Surital also produced a greater elevation in blood pressure during the maintenance period and a higher incidence of dizziness during the recovery period. A greater total amount of thiopental was required to achieve the end point of intubation than was necessary with Surital. The relative actions of these 2 agents have now been studied critically in a joint investigation in several clinics, and it does appear that the differences between the anesthetic syndromes in man are insignificant.

Surital sodium is injected intravenously in 2.5 per cent solution. From 3 to 6 ml. of a freshly prepared solution are injected at a rate of 1 ml. every 5 seconds. As indicated, additional injections of 0.5 to 1.0 ml. may be made intermittently with the needle remaining in the vein. The maximal total dose should not exceed 1 gm. or 40 ml. of a 2.5 per cent solution.

**Methohexital Sodium (Brevital Sodium).** Unlike the foregoing intravenous anesthetics, methohexital is a barbiturate and not a thiobarbiturate. Chemically, the compound is sodium *α-dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate. The usual dosage range for induction of anesthesia is 5 to 12 ml. of a 1 per cent solution. Recovery from anesthesia with methohexital is exceptionally prompt. It finds extensive use in dental procedures.

It does appear that methohexital enjoys extended use and has been accepted as an intravenous anesthetic for short surgical procedures. Rapid emergence, with a minimum of residual depression, appears to be its principal advantage.

**Intravenous steroid anesthesia. (Viadril).** This agent is not presently generally used. For a discussion, see page 505, 5th edition.

### MUSCLE RELAXANTS IN ANESTHESIA

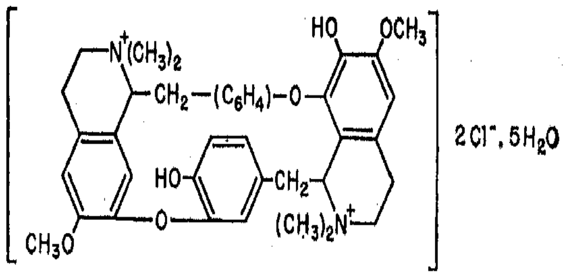
**Curare** is not an anesthetic. It is considered along with the anesthetic agents because its principal use in medicine lies in the field of general anesthesia.

The word *curare* is a generic term applied rather generally to many South American arrowhead poisons. It was used by the early physiologist Claude Bernard and also by François Magendie. The poisons are distributed among several South American plants including varieties of *Strychnos* and *Chondodendron*. Until recently the material had no use in clinical medicine. It was an interesting tool in the hands of pharmacologists. It produces paralysis of skeletal muscle at the neuromuscular junction. The product was marketed as a dark brown plant extract. It was of variable composition, and its dosage was not dependable. Commenting on curare a century ago Bernard wrote: "Not only is it necessary to isolate chemically the active principle of curare from the extraneous substances with which it is mixed; it is necessary besides, to determine what type of physical or chemical modification this toxic substance imposes on its site of action in order to effect its paralytic action." It took a hundred years to meet this challenge; in 1935 King determined that the active principle is a quaternary base, *d*-tubocurarine or tubocurarine. In 1942 the possibilities of this substance as a relaxant to supplement anesthesia were explored.

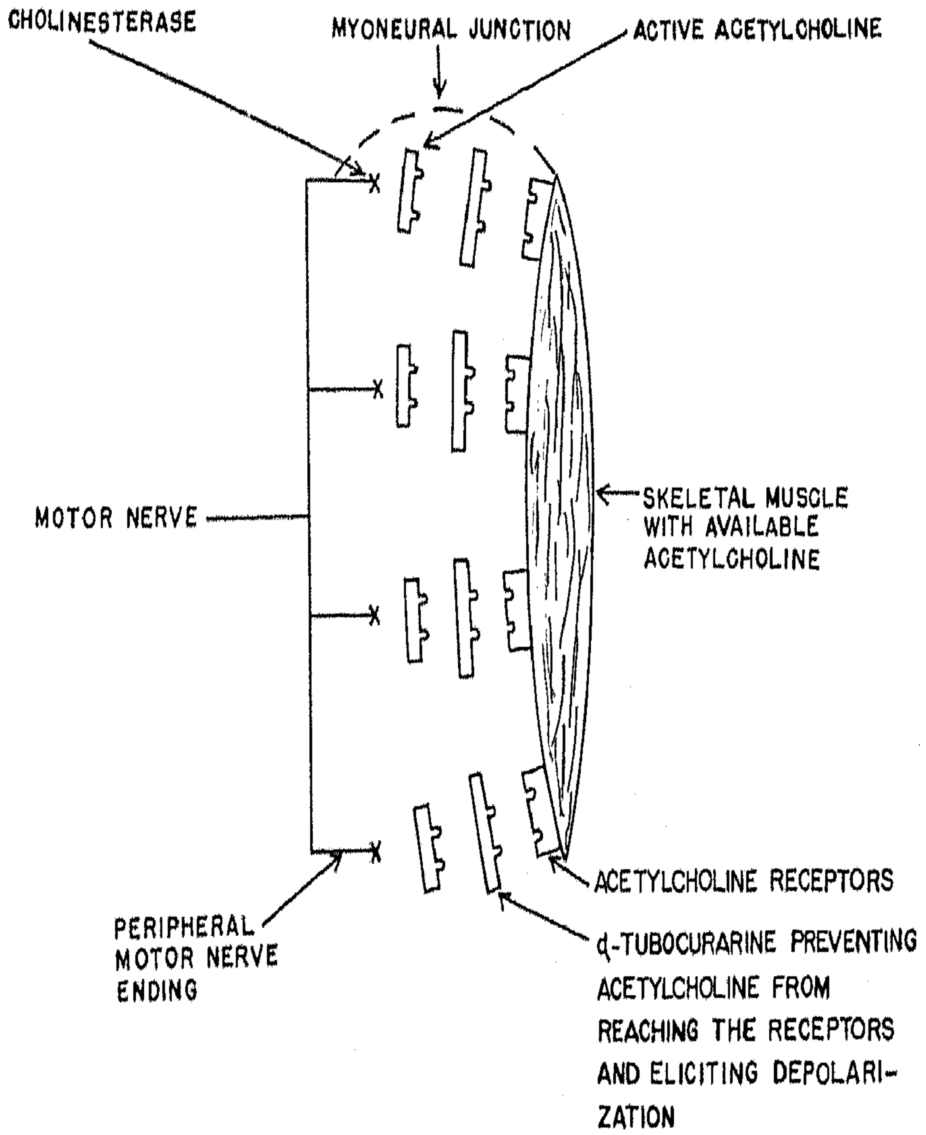
**Tubocurarine Chloride, U.S.P.** The active principle of curare, *d*-tubocurarine, has been isolated and synthesized. The chloride of this quaternary ammonium base is a white or yellowish-white powder which is water soluble. This substance produces a paralytic effect on neuromuscular conduction. Tubocurarine elicits this response without other marked untoward pharmacologic effects. The principal site of action of tubocurarine is the neuromuscular junction of skeletal musculature. It blocks the activity of acetylcholine which initiates muscle contraction at this site. The muscles are affected in the following order: (1) those innervated by the cranial nerves; (2) muscles of the trunk and extremities; and (3) muscles of respiration (the diaphragm is affected last).

**Action of *d*-tubocurarine at the neuromuscular junction.** When skeletal muscle activity is depressed by *d*-tubocurarine, there is a reduction in the amplitude of the propagated action potential of the muscle. Recovery of the action potential is accompanied by the return of the contractile response of the muscle. After a paralytic dose of *d*-tubocurarine, peripheral nerve function is not impaired. One concludes, therefore, that the site of action is the neuromuscular junction.

Eccles *et al.* (1941) characterized the end plate potential of skeletal muscle as a *gradually decaying local depolarization of the muscle membrane*. They demonstrated that curare diminished the amplitude and detonating potential, ultimately reducing it to a subthreshold depolarization. In the antagonism of this effect of curare by prostigmine, the latter compound served to prolong the junctional negativity. This action is mediated through the inactivation of cholinesterase; this makes available at the neuromuscular junction additional acetylcholine. Acetylcholine when applied at the end plate of a muscle fiber establishes a train of propagated impulses. Kuffler (1943) showed that this activity resulted from the local depolarization of the end-plate locus. Thus, the neuromuscular junction paralytic effect of *d*-tubocurarine results from an *impedance of end-plate depolarization*. The site of action of *d*-tubocurarine in blocking acetylcholine at the neuromuscular junction is shown schematically in figure 22-3.



Tubocurarine Chloride, U.S.P.

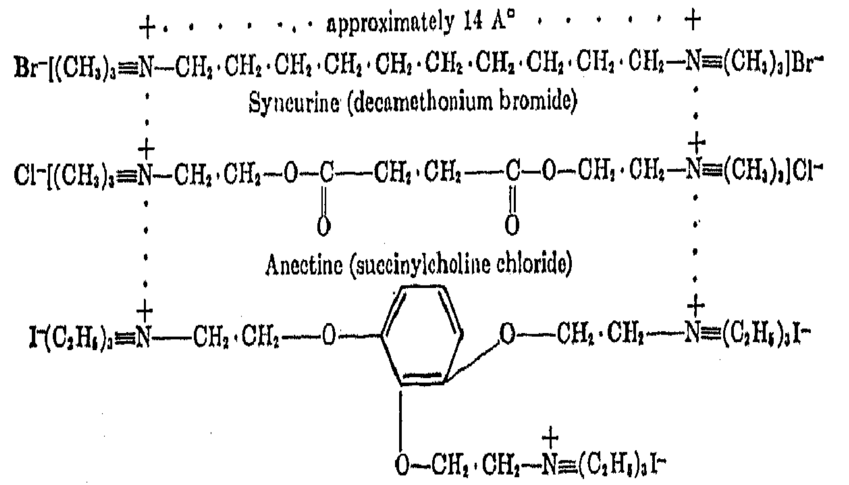


CHOLINESTERASE
MYONEURAL JUNCTION
ACTIVE ACETYLCHOLINE
MOTOR NERVE
SKELETAL MUSCLE WITH AVAILABLE ACETYLCHOLINE
ACETYLCHOLINE RECEPTORS
PERIPHERAL MOTOR NERVE ENDING
d-TUBOCURARINE PREVENTING ACETYLCHOLINE FROM REACHING THE RECEPTORS AND ELICITING DEPOLARIZATION

FIG. 22-3. Schematic Action of Neuromuscular Blockade

It has been well established that the contraction of skeletal muscle is accompanied by a loss of potassium ions. At the neuromuscular junction potassium and *d*-tubocurarine appear to compete for the same receptors. It has been demonstrated that the potassium ion elicits a decurarizing action on skeletal muscle. Ing (1936) and other investigators believed that the onium ion, which functions like the ion of an alkali metal, is responsible through its specific physicochemical properties of competing with the potassium ion at the neuromuscular junction. This does not appear to be an adequate hypothesis because certain compounds containing tertiary nitrogen atoms may serve as blocking agents of high potency. A definitive explanation for the blocking action of these onium compounds on a molecular basis has not yet been produced.

It is interesting to compare the structures of the curariform compounds as shown in the formulas, page 338, noting the uniform distance in separation of the 2 quaternary nitrogen atoms. The same distance prevails in the spacing of the nitrogen atoms in *d*-tubocurarine. Of special interest is the fact that Syncurine, although a neuromuscular blocking agent, produces its blockade through a different mechanism, see page 341. Its blockade is not antagonized by potassium ions.


approximately 14 A°
Syncurine (decamethonium bromide)
Anectine (succinylcholine chloride)

Flaxedil (1,2,3-tris-(diethylaminoethoxy) benzene triethiodide)
*Structures of Commonly Used Curariform Drugs. Dotted Lines Show the Approximate Distance between the Quaternary Nitrogen Atoms*

**Other actions and fate of *d*-tubocurarine.** Many investigators have studied the over-all effect of *d*-tubocurarine on unanesthetized subjects. Harris (1951) observed 243 such cases. During the period of muscle paralysis, hearing was unaffected, smell was relatively accurate, and touch and pressure sensations were present. With as much as 30 mg. of the drug, consciousness was not lost, and pain stimuli were present. Thus, it may be concluded that *d*-tubocurarine has no narcotic action.

*d*-Tubocurarine produces vagal block similar to atropine. The blockade of *d*-tubocurarine extends also to autonomic ganglia, but this action is elicited by dosage levels that are higher than those required for neuromuscular blockade. *d*-Tubocurarine stimulates the spinal centers, but this action is masked by its more powerful peripheral action at the neuromuscular junction. Riker and Wescoe (1951) showed that *d*-tubocurarine will desensitize the heart to challenging doses of epinephrine when the subject is under cyclopropane anesthesia.

One of the untoward actions of *d*-tubocurarine is caused by its capacity to release histamine from tissues. This may occur in sufficient quantity to evoke bronchospasm.

*d*-Tubocurarine is not absorbed from the gastrointestinal tract to any appreciable extent. Absorption is prompt from subcutaneous and intramuscular injection sites. The drug is given intravenously for muscle relaxation in anesthesia. It is not concentrated at the neuromuscular junction but widely distributed through the body. A portion of the dose of *d*-tubocurarine is excreted by the kidney in the urine, and the remainder is metabolized by the liver. In the blood it is not bound by plasma proteins. A single intravenous dose produces paralysis of skeletal muscle for 20 to 30 minutes, then the effect diminishes although some influence of the drug may persist for an entire day.

***d*-Tubocurarine in anesthesia.** The intravenous use of *d*-tubocurarine chloride 3 to 9 mg. produces complete abdominal relaxation. It is most satisfactorily administered by fractional dosage. It serves as a good supplement for cyclopropane, nitrous oxide, thiopental sodium, and ether anesthesias. With ether anesthesia only ⅓ of the dose is required. Thus this agent makes it possible to obtain more satisfactory relaxation with the foregoing anesthetic agents in the lighter anesthetic planes; this enables suitable anesthesia to be achieved with a lesser concentration of the anesthetic agent. This diminishes the possibility of serious postanesthetic sequelae in seriously ill patients.

**Gallamine Triethiodide (Flaxedil),** is another skeletal muscular relaxant that acts similarly to *d*-tubocurarine. Chemically, Flaxedil is 1,2,3-tris-(diethylaminoethoxy)-benzene triethiodide as shown above. Flaxedil occurs as a white or slightly yellow powder. The compound is slightly hygroscopic and is readily soluble in water.

**Flaxedil on skeletal muscle and other organs.** The mechanism of action of Flaxedil in relaxing skeletal muscle is similar to that of *d*-tubocurarine. Quantitatively its activity is ⅕ to ¼ that of *d*-tubocurarine although it is somewhat more prolonged. One of the principal differences between the response to Flaxedil and that of *d*-tubocurarine is their blood pressure effect. *d*-Tubocurarine causes a fall in blood pressure; Flaxedil may elicit no effect or cause a slight increase in blood pressure. Flaxedil produces vagal blockade similar to atropine. The vagal action of Flaxedil is more powerful than that of *d*-tubocurarine. This vagal effect of Flaxedil is its only atropine-like action. Unlike *d*-tubocurarine, it does not affect any autonomic ganglia. The stimulating action on the spinal cord elicited by *d*-tubocurarine is not shared by Flaxedil. Neither does Flaxedil cause the release of any appreciable amount of histamine and consequent bronchospasm. Like *d*-tubocurarine, Flaxedil is antagonized by neostigmine and edrophonium. Its order of skeletal muscle paralysis essentially follows that of *d*-tubocurarine. For this purpose it is generally used concomitantly with cyclopropane, or with an intravenous thiobarbiturate and nitrous oxide and oxygen (Foldes *et al.*, 1952 and 1954). With ether anesthesia (as with *d*-tubocurarine) less Flaxedil is required to achieve relaxation. The relaxation achieved by 80 mg. of Flaxedil is comparable to that produced by 15 mg. of *d*-tubocurarine. Flaxedil may produce tachycardia of such a degree as to interdict its use in thyrotoxic or cardiac patients. Flaxedil will desensitize the heart to a challenging dose of epinephrine when the subject is under anesthesia with hydrocarbons such as cyclopropane.

**Use of Flaxedil.** Flaxedil is used like *d*-tubocurarine to produce increased muscular relaxation during anesthesia. Flaxedil is administered intravenously; the average initial dose is about 100 mg. This may be augmented during the course of the anesthesia.

**Dimethyl-tubocurarine Iodide, N.F. (Metubine Iodide).** The molecule of *d*-tubocurarine contains 2 phenolic hydroxyl groups. By replacing the hydrogen atoms of these 2 groups with methyl radicals, the dimethyl ether is formed. Dimethyl-tubocurarine iodide is a stable, white crystalline solid. It is readily soluble in water, to which it imparts a slightly acid reaction.

The pharmacologic response elicited by dimethyl-tubocurarine is similar to that of *d*-tubocurarine chloride, page 336. As a skeletal muscle relaxant, dimethyl-tubocurarine is more potent and longer acting than *d*-tubocurarine. However, it depresses the respiratory muscles to a lesser extent than does *d*-tubocurarine. Dimethyl-tubocurarine has a greater margin of safety.

Dimethyl-tubocurarine iodide is used in anesthesia to increase the degree of muscular relaxation, similar to *d*-tubocurarine. Clinically, upon intravenous administration 1 mg. of dimethyl-tubocurarine evokes a response comparable to 3 mg. of *d*-tubocurarine. The average initial dose varies with the anesthetic agent employed with the muscle relaxant. With ether anesthesia the dose is 1.5 to 3 mg., with nitrous oxide 4 to 6 mg., with cyclopropane 2 to 4 mg., and with thiopental sodium 4 to 6 mg. In case of excessive dosage the antidote for *d*-tubocurarine, namely, edrophonium (Tensilon) or neostigmine, should be administered.

**Succinylcholine Chloride U.S.P. (Anectine Chloride, Sucostrin Chloride).** This compound is an ultra-short relaxant of skeletal muscle. The substance chemically is diacetylcholine chloride, inasmuch as the molecule contains 2 molecules of acetylcholine chloride linked at the alpha methyl groups, as shown on page 338.

Succinylcholine chloride occurs as a white crystalline solid. It is readily soluble in water, to which it imparts a slightly acid reaction.

**Pharmacologic action of succinylcholine chloride.** Succinylcholine chloride is a depolarizing skeletal muscle relaxant. In this respect its action resembles that of Syncurine, p. 341. Its action at the neuromuscular junction resembles that of acetylcholine. The first evanescent effect is that of stimulation of certain of the muscle fibers. This is followed immediately by a flaccid paralysis and a blockade of neuromuscular conduction. Evans *et al.* (1952) postulated that the effect of succinylcholine is due to the rapid selective inhibition of the true cholinesterase of the neuromuscular junction. Consequently, the persistence of the action of the acetylcholine present causes prolonged depolarization of the motor end-plates. Succinylcholine is hydrolyzed by the pseudocholinesterase of plasma.

Neostigmine and edrophonium, which terminate the activity of *d*-tubocurarine chloride, do not combat the action of succinylcholine. They actually intensify it.

**Therapeutic uses of succinylcholine.** Succinylcholine is used in anesthesiology to produce crucial, transient skeletal muscle relaxation or prolonged relaxation by infusion. It is valuable in *endotracheal intubation*, *direct laryngoscopy*, *bronchoscopy* and *esophagoscopy*.

The compound is administered in single doses intravenously or continuously in small doses. The average dose for relaxation of short duration is 20 mg. The optimal dose for various individuals varies between 10 and 30 mg. Muscle paralysis occurs within 1 minute. It persists for only 2 to 4 minutes.

**Intravenous infusion of succinylcholine.** The prompt subsidence of the muscular relaxant action of succinylcholine has led to its use by intravenous infusion for controllable skeletal muscle relaxation during anesthesia. Succinylcholine is dissolved in 5 per cent glucose solution or normal salt solution. The strength favored by most anesthesiologists is 0.1 or 0.2 per cent. The desired stage of muscle relaxation is achieved by allowing the solution to flow at a rate of 2 to 4 ml. per minute. The quantity varies considerably from patient to patient.

Controlled relaxation may be maintained throughout the surgical procedure without producing apnea by the careful regulation of the flow of succinylcholine. Fasciculations during the early stages of succinylcholine infusion indicate too rapid a flow of the relaxant. As stated previously, prompt recovery follows the discontinuance of the infusion of succinylcholine.

Davis *et al.* (1955) observed prolonged muscular weakness in about 13 per cent of their patients who had received succinylcholine as a muscular relaxant under nitrous oxide anesthesia. The weakness was experienced principally in the muscles of respiration. They were able to demonstrate the same syndrome in dogs receiving succinylcholine which were ventilated with 20 per cent carbon dioxide. Hypercapnia causes potassium ion release from muscle; this ion antagonizes the action of succinylcholine. They suggest that if hypercapnia is allowed to persist in the anesthesized patient the neuromuscular junction of skeletal muscle may become more sensitive to such blocking agents as succinylcholine.

Foldes *et al.* (1956) reviewed the subject of succinylcholine apnea. They conclude that this is not a pathological entity but a syndrome that may be attributed to a number of conditions. It appears to occur most frequently in debilitated chronically ill individuals, usually associated with a serious gastrointestinal lesion with fluid and electrolyte imbalance. Many other conditions are cited that may contribute to succinylcholine apnea, yet occasionally it can occur in seemingly healthy individuals. Foldes *et al.* state, "If succinylcholine is used correctly and respirations are assisted rather than controlled, succinylcholine apnea is a preventable complication." However, Foldes *et al.* (1963) noted in a study of 20 patients who developed prolonged apnea after intravenous administration of succinylcholine only 4 had normal levels of plasma cholinesterase. They felt that succinylcholine-prolonged apnea is frequently but not always associated with the presence of atypical plasma cholinesterase.

Borders *et al.* (1955) studied the cholinesterase of whole blood and plasma in relation to succinylcholine hydrolysis. The esterase level was not diminished by anesthetic agents. Concentrated plasma cholinesterase given parenterally was found to shorten the period of apnea produced by a fixed amount of succinylcholine. They found, however, no evidence to justify the administration of cholinesterase to patients who were exhibiting a prolonged respiratory depression following the administration of succinylcholine.

Kalow and Lindsay (1956) showed that the plasma cholinesterase of a normal adult is capable of hydrolyzing up to 120 mg. per minute of succinylcholine chloride *in vitro*. The rate of destruction of succinylcholine at any given concentration is a function of the plasma concentration of cholinesterase. In order to exert its action at the neuromuscular junction, succinylcholine must enter the extravascular space to escape hydrolysis by plasma cholinesterase.

Beretervide (1955) observed that succinylcholine produced profound bradycardia by central vagal stimulation when injected into conscious animals. Fortunately the bradycardia is abolished by general anesthesia. Atropine and bilateral vagotomy also block this effect. Succinylcholine was found to elicit no direct actions on the blood vessels or the heart. Heymans and DeVleeschhouwer (1958) showed that curarizing doses of succinylcholine administered to dogs, in one dose or by infusion, evoked no effect upon the blood pressure. Likewise, there was no evidence of depression on the mechanisms of blood pressure homeostasis.

Helmsworth and Schotz (1955) critically studied succinylcholine in a large series of patients. They comment, "No unwanted side effects were observed." They are of the opinion that this agent is superior to other neuromuscular blocking drugs.

Succinylcholine is the drug of choice to produce relaxation in electroshock and other types of convulsive therapy.

It is the opinion of the authors that this type of controlled relaxation represents a distinct advance in the production of muscular relaxation for surgery. It appears to be replacing all other types of skeletal muscle relaxants.

**Decamethonium bromide, C10 (Syncurine).** Barlow and Ing (1948) of Oxford University developed the concept that the marked potency of tubocurarine chloride was likely due to the presence of 2 quaternary nitrogen groups in one molecule, spaced at an optimal distance. Several interesting compounds were prepared and studied. The most active compound had a structure in which the 2 nitrogen atoms were separated by 10 carbon atoms as shown on page 338.

The pharmacology of Syncurine was investigated by Castillo and deBeer (1949). Essentially, their findings demonstrated that Syncurine is more potent than tubocurarine as a relaxant of skeletal muscle. Its action is peripheral like that of *d*-tubocurarine. Syncurine elicited less respiratory paralysis than did *d*-tubocurarine. The relaxant action of Syncurine is not antagonized by Neostigmine or edrophonium, page 342. Chronic toxic effects were not produced by repetitious injections of Syncurine over a period of a month. Syncurine evokes a depolarization of the end-plate region that is sufficiently profound and prolonged to discharge and depolarize the adjacent muscle membrane. Its action appears to be identical with that of acetylcholine, but since it is not hydrolyzed by cholinesterase, the action endures.

The clinical studies in anesthesia with Syncurine in England by Hewer *et al.* (1949), and in America by Dripps and others (1953), were very favorable. The principal favorable observation appears to be that unlike *d*-tubocurarine, Syncurine did not produce histamine-like side effects such as a fall in blood pressure and bronchospasm. The relaxation produced by Syncurine was more prompt and of shorter duration than that evoked by *d*-tubocurarine.

Spencer and Coakley (1955) studied the effect of Syncurine administered in more than 6000 anesthesias. Their mortality rate with the agent was 1 in 6215. They emphasize the necessity for adequate oxygenation of the patient and also advocate the use of low dosage levels of Syncurine. Their most satisfactory results were obtained in lower abdominal operations of short duration, endotracheal intubation, and endoscopy. The properties of Syncurine which impressed these observers were *rapidity and shortness of duration of action*, *tachyphylaxis*, *absence of histamine response*, *variability of individual reaction*, and *depression of respiration*.

The theoretical concepts prompting its synthesis are appealing. The fact that no specific antidote is available to combat excessive relaxation produced by Syncurine has militated against its general acceptance. It appears that its use is waning.

Syncurine is administered intravenously (1 mg. per minute); the full relaxant dose is 2 to 2.5 mg. This dose may be further supplemented.

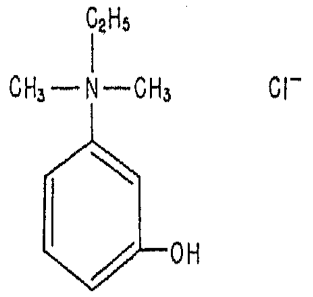
**Syncurine and *d*-tubocurarine.** At the neuromuscular junction, *d*-tubocurarine and Flaxedil produce muscle paralysis by an impedance of end-plate depolarization, page 336. Syncurine has a stimulant action on skeletal muscle that is not shared by *d*-tubocurarine. There appears to be an inverse relationship between the conditions of sensitivity to Syncurine and those for sensitivity to *d*-tubocurarine (Paton, 1951). Neuromuscular block elicited by Syncurine is stable; that produced by *d*-tubocurarine is labile. It appears that the *d*-tubocurarine block is due to a blocking of the chemical transmitter acetylcholine, resulting in an impedance of depolarization. The block produced by Syncurine follows an abnormally prolonged transmitter-like action, in which initial excitation passes over rapidly into inexcitability.

The difference in the character of the 2 types of neuromuscular blockage is clearly shown by the following experiment in cats. When Syncurine is given first and followed by *d*-tubocurarine, there is no antagonism exhibited between the 2 muscle relaxants. On the other hand, if *d*-tubocurarine is administered first and followed by Syncurine, it will antagonize the action of *d*-tubocurarine and restore the muscle to normal contraction (Hutter, 1952).

**Relative potencies of neuromuscular blocking agents.** Hoppe (1955) studied the relative potencies of the various neuromuscular blocking agents in laboratory animals. He found that among the agents studied there was a marked variation in their potencies in different species of laboratory animals. He estimated the effective median intravenous doses for man relative to *d*-tubocurarine as divalent cation = 1. His data are as follows: *d*-tubocurarine chloride pentahydrate 0.160 mg./kg., Metubine iodide 0.038 mg./kg., Flaxedil 1.115 mg./kg., decamethonium iodide 0.044 mg./kg., and succinylcholine iodide 0.440

mg./kg. These data are reflected in the recommended doses of the respective agents.

**Edrophonium, U.S.P. (Tensilon).** This substance is used mainly to antagonize the action of curare and curare-like compounds. It is N-ethyl-N-(*m*-hydroxyphenyl)-N,N-dimethyl-ammonium chloride, as shown in the accompanying formula.



Edrophonium, U.S.P.
Tensilon

The compound occurs in crystals which are readily soluble in water. Edrophonium is superior to Neostigmine in antagonizing curare and Flaxedil muscular paralysis. It elicits a minimal effect on the smooth muscle of the intestines. Its cholinergic activity is approximately one-hundredth that of Neostigmine. The antagonism of *d*-tubocurarine and edrophonium is shown in figure 22-4 (Randall, 1951).

An examination of the structure of edrophonium reveals that it is a quaternary ammonium salt like *d*-tubocurarine and Flaxedil. Like most quaternary salts it might be expected to elicit a curariform action. This it does in animals at toxic levels and produces death by respiratory failure. The safety margin between the antagonizing dose to curare and its curariform action is from 40- to 80-fold. Edrophonium in therapeutic doses resembles acetylcholine in its stimulating properties on skeletal muscle. Edrophonium potentiates the twitch tension of muscle which is stimulated electrically through its nerve.

Edrophonium is administered intravenously to combat excessive muscle paralysis of *d*-tubocurarine or Flaxedil in 10 mg. (1 ml.) doses. This dosage may be repeated whenever necessary. Morris *et al.* (1953) pointed out that the action of edrophonium is evanescent compared to that of *d*-tubocurarine. The patient who has received edrophonium should be watched carefully and if the respiratory depression of excessive curarization should supervene after the effect of edrophonium has been dissipated, the dose of the latter should be repeated.

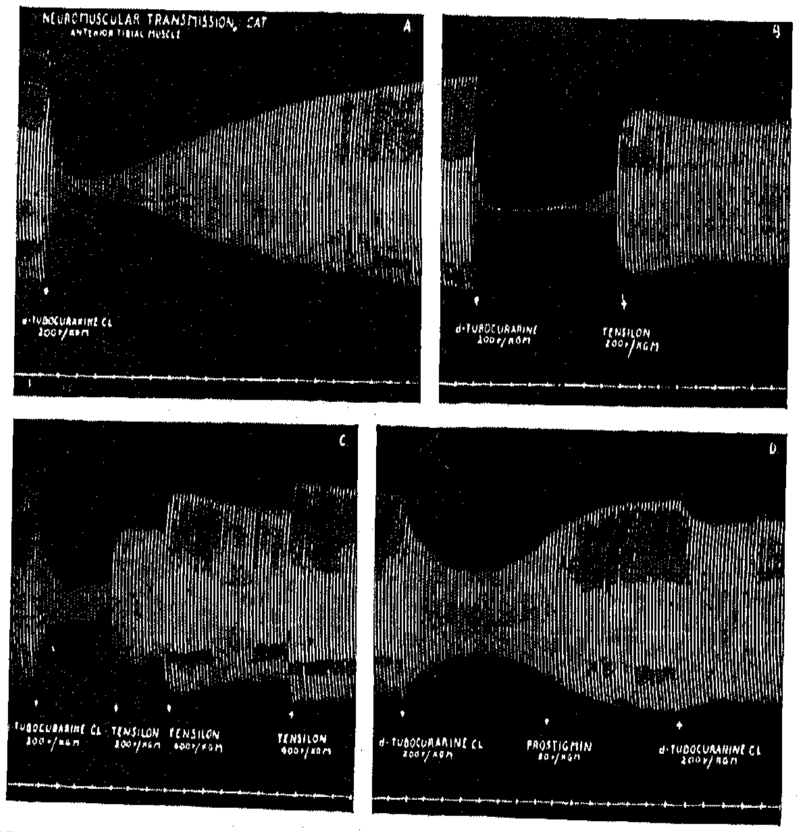


FIG. 22-4. Neuromuscular blocking action of *d*-tubocurarine chloride and the antagonizing effects of Tensilon and Prostigmin. Contraction of the anterior tibial muscle (indirect stimulation, 7 times per minute). Time in minutes. Cat under Dial-urethane anesthesia. Three minutes elapsed between *A* and *B*; 14 minutes between *B* and *C*; and 4 minutes between *C* and *D*.

### SPINAL ANESTHESIA

The use of local anesthetic agents in the spinal canal dates back to the turn of the century At this time cocaine hydrochloride was the only available local anesthetic agent. Because of its toxicity many accidents occurred, and this method of producing muscular relaxation lost popularity. However, with the advent of the newer synthetic local anesthetics a revival of interest took place in spinal anesthesia. Today it is one of the most generally used procedures to produce muscular relaxation for surgery.

Under the section on local anesthesia it was learned that the injection of solutions of local anesthetic agents around a nerve will block the passage of impulses over the nerve fibers. *Spinal anesthesia is a nerve root block, which anesthetizes the spinal nerves at the point of their exit from the intervertebral foramina.*

**Characteristics of spinal anesthesia.** All types of nerves are blocked in spinal anesthesia. The order of effect is as follows:

1. Sensory fibers
2. Sympathetic fibers
3. Motor fibers

The motor fibers are the last paralyzed by the anesthetic agent and are usually the first to recover. The sensory blocking occurs in 6 to 8 minutes. The full effect, including motor fibers, takes place in 10 to 15 minutes.

The blocking of the sensory fibers carrying different sensations to the brain occurs in the following order:

1. Loss of sensation of heat and cold
2. Loss of cutaneous and pressure pains
3. Loss of joint sense, pressure sensation and touch

In the spinal fluid the local anesthetic disappears very rapidly. With procaine 70 per cent of the agent injected disappears in 5 minutes, and after a half hour only traces remain.

The distribution and fate of spinal anesthetics were investigated by Howarth (1949). Procaine was brominated with radioactive bromine. The dibromoprocaine hydrobromide was used in cats and monkeys. After intrathecal injection the concentration in the spinal subarachnoid space rapidly declined. This was accompanied by a high urinary excretion rate. The blood concentration remained consistently low. After intrathecal injection of the radioactive agent, only the spinal roots showed any uniform capacity to concentrate the compound above its level in the cerebrospinal fluid. Radioactive dibromoprocaine was shown to enter the spinal cord after intrathecal injection. Howarth points out that the agent left the cerebrospinal fluid mainly by the venous system. The esterase in the blood which rapidly hydrolyzes procaine does not exist in the spinal fluid (Foldes and Aven, 1952).

**Blood pressure.** The blocking of the sympathetic fibers which control arteriolar constriction is responsible for a fall in blood pressure when a spinal anesthetic is administered.

The relaxation of skeletal musculature under spinal anesthesia is complete. This also contributes to the decrease in blood pressure. Severe hypoxia may also contribute to the blood pressure fall. The fall in blood pressure is progressive because of the fact that the reflex control of the sympathetic system is abolished. The higher the anesthetic progresses in the spinal canal, the greater is the fall in blood pressure. When anesthesia reaches the clavicle, the carotid sinus reflex is lost, and the fall in blood pressure is marked and continued. Seevers and Waters (1932) showed that serious cardiovascular changes occur with greater frequency in anesthesias which are high enough to involve the thorax. Blocks of this type involve not only the sympathetic vasoconstrictor fibers but also the intercostal nerves.

The fall in pressure is combated by the use of the sympathomimetic amines ephedrine or phenylephrine (fig. 22-5).

Bradycardia is very prominent during spinal anesthesia. This is probably associated with increased vagus tone. It permits complete diastolic filling of the heart and improves the stroke volume. Seevers and Waters (1932) observed in dogs a rise in venous blood pressure during spinal anesthesia.

A tachycardia during spinal anesthesia must be considered a possible danger signal. It is probably the result of hemorrhage. The blood volume should be immediately augmented by whole blood or plasma, for patients under spinal anesthesia are less tolerant to blood losses.

The fall in blood pressure under spinal anesthesia is a function also of the dose of the anesthetic agent. This was shown by CoTui (table 22-3). High spinal anesthesia may produce somnolence in the patient due to diminished cerebral blood flow. Kety *et al.* (1950) showed that during high spinal block in man the cerebral blood flow dropped from 52 to 46 ml. per 100 gm per minute. It is possible also that a small fraction of the dose

| | **Ephedrine** | **Mephentermine** | **Desoxyephedrine** | **Methoxamine** | **Phenylephrine** |
|---|---|---|---|---|---|
| **Synonyms** | | **Wyamine** | **Methedrine**<br>**Methamphetamine** | **Vasoxyl** | **Neosynephrine** |
| **Stability** | Base Decomposes HCl Stable | Stable | Stable | Stable | Oxidizes Easily |
| **Action** | Adrenergic on Effector Cells | Same | Same | Same | Same |
| **Elimination** | Slowly Destroyed in Liver | Metabolized Oxidized | Slowly Destroyed or Eliminated | Destroyed or Eliminated | Oxidized |
| **Central Stimulation** | Some Tremor and Excitement | Present but of Low Order | Marked | None | Slight |
| **Cardiac Rate** | Accelerated | Unchanged or Slowed | Accelerated | Slowed, often Markedly | Slowed |
| **Cardiac Output** | Increased Contractility | No Change | Increased | No Change | Increased |
| **Tendency to Arrhythmias** | Increased Tendency to Auricular Fibrilation | None | Occasional Auricular Fibrilation | Bradycardia with Large Doses | None |
| **Effect on Coronaries** | Dilated and Increased Flow | Increased Flow | Dilated | Dilated | Dilated |
| **Systolic Pressure** | Elevated | Elevated | Elevated | Elevated | Elevated |
| **Diastolic Pressure** | Slightly Elevated | Slightly Elevated | Elevation or None | Elevated | Elevated |
| **Average Dose Intramuscular Intravenous** | 50 mg.<br>15-25 mg. | 35 mg.<br>15-30 mg. | 20 mg.<br>5-10 mg. | 15 mg.<br>5 mg. | 3-5 mg.<br>0.25-0.5 mg. |

FIG. 22-5. Sympathomimetic amines in the hypotension of spinal anesthesia (Anderson 1964)

TABLE 22-3

*Relation of Procaine Dosage to Blood Pressure in the Dog*

(CoTui, 1936)

| Exp. No. | Dose Procaine HCl | Lowest Blood Pressure | Time of Recovery to 100 mm. Hg |
|---|---|---|---|
| | *mg.* | *mm. Hg* | *min.* |
| 1 | 250 | 96 | 52 |
| 2 | 300 | 68 | 74 |
| 3 | 600 | 52 | 106 |
| 4 | 700 | 32 | 134 |
| 5 | 800 | 22 | 192 |

of the agent administered may appear in the ventricular fluid and affect the state of consciousness (Greene, 1955).

Richardson and Walton (1953) conducted studies which extended our knowledge with regard to the action of spinal anesthetics on blood pressure. They used dogs without premedication and injected into the subarachnoid space ($L_5$—$S_1$) 20 to 62 mg./kg. of procaine hydrochloride. The injection elicited an increase in the contractile force and rate of beat of the heart, an increase in arterial pressure, depression of gut activity, and other effects which mimic the response to epinephrine. The effects were not elicited in adrenalectomized animals. They were obliterated also by thiopental anesthesia. The epinephrine-like response is not produced by procaine intrathecally 2 to 20 mg./kg. These investigators interpret their findings to indicate that the effect of large doses of procaine intrathecally appears to be due to the passage of procaine into the circulation. This produces cerebral excitation with the subsequent release of epinephrine. This syndrome is seldom experienced clinically with a sedated patient and a lower dosage level of procaine.

**Respiration.** Respiratory failure may be the cause of death during spinal anesthesia. The mechanism of respiratory paralysis may occur as follows:

1. Block of the intercostal and phrenic nerves
2. Direct action of the anesthetic agent on the medulla by ascending diffusion of the solution
3. Insufficient blood supply to the respiratory centers resulting from a profound fall in arterial blood pressure

The principal danger of respiratory embarrassment is that of intercostal and phrenic nerve paralysis. If 10 mg. of procaine in a viscid solution are injected into the spinal canal at the level of the third cervical vertebra, the diaphragm is paralyzed, but there occurs increased activity of the intercostal nerves. An injection, into the cisterna magna will cause paralysis of both the diaphragm and the intercostal nerves. This is very probably due to direct action on the respiratory centers. When an anesthetic solution ascends in the spinal canal, there is a progressive paralysis of the spinal nerve roots of the respiratory muscles.

Hill and MacDonald (1935) injected local anesthetic solutions directly into the fourth ventricle of dogs and cats. Prompt respiratory failure of the central type occurred. Intravenous solutions of procaine 50 to 70 mg./kg. produced respiratory paralysis, which is characteristically central.

**Technic of spinal anesthesia.** The solution of the local anesthetic is injected into the subarachnoid space between the *conus medullaris* and the terminal portion of the spinal cord. The patient is generally in an erect, prone, or lateral position. The spine is flexed to widen the interspinous spaces. A line drawn between the highest points on the iliac crests crosses the spine at the fourth lumbar vertebra.

After sterilization of the skin, a small quantity of local anesthetic may be injected subcutaneously (*procaine hydrochloride 2 per cent with epinephrine or some other similar vasoconstrictor*) to lessen the pain of the insertion of the spinal needle. A needle about 5 cm. long is then inserted through the interspinous space. Spinal fluid equal in volume to the volume of anesthetic agent to be injected is withdrawn. This prevents increased pressure in the spinal canal and danger of medullary embarrassment. The anesthetic is then injected. The speed of injection determines to some extent the distance to which the anesthesia will extend. Rapid injections produce high anesthesia.

The spinal fluid into which the anesthetic agent is injected has the following characteristics:

Specific gravity, 1.003 to 1.008
pH, 7.35
Total volume, 150 ml.
Total volume in cord, 20 ml.
Average pressure (recumbent), 110 mm. $H_2O$

The following are the dosage levels for different heights of anesthesia for procaine hydrochloride.

*Dose in Milligrams of Procaine Hydrochloride*

| Perineum | Lower Abdomen | Mid Abdomen |
|---|---|---|
| 100 in 3 ml. | 120 in 5 ml. | 120 in 5 ml. |
| $L_3$ | $L_2$ | $L_1$ |

*Procaine* (page 230) produces anesthesia for about 1 hour. *Tetracaine* or *Pontocaine* is more lasting. Relaxation will persist for 2 to 3 hours with the latter drug. With Tetracaine (page 238) 10 to 20 mg. are administered dissolved in 1 to 2 ml. of fluid. Bonica and Backup (1950) found that the addition of epinephrine or phenylephrine hydrochlorides to procaine hydrochloride solution prolonged the spinal anesthesia about 50 per cent. In their cases postanesthetic sequelae were not increased by the addition of a vasoconstrictor to the spinal anesthetic.

Table 22-4 gives the dosage and duration of response of the more generally used spinal anesthetic agents.

The anesthetic solution usually has a greater density than the spinal fluid. Its diffusion can be controlled by the position of the patient. A horizontal position minimizes diffusion. The lowest position of the spinal canal is midthoracic. The level of anesthesia can be raised by placing the patient in the Trendelenberg position to facilitate the diffusion of the solution of the anesthetic.

TABLE 22-4

*Data on Action of Five Local Anesthetics*

(Featherstone, 1958)

| | Usual Concentrations | Volume of Solution | Range or Maximum Dose | Relative Promptness | Duration |
|---|---|---|---|---|---|
| | % | *ml.* | *mg.* | | *hr.* |
| Procaine | 3.0–5.0 | 2–5 | 50–200 | 2 | 1–1½ |
| Tetracaine | 0.3–0.5 | 3–5 | 10–15 | 2 | 3–5 |
| Piperocaine | 3.0–4.0 | 3–5 | 50–200 | 2 | 2+ |
| Dibucaine | 0.05–0.25 | . . . | 3–13 | 3 | 4–6 |
| Lidocaine | 2.0–4.0 | 4 | 150 | 1 | 2½–3 |

In general, more concentrated solutions of the local anesthetic result in longer anesthesia, greater relaxation, and possible permanent damage to nerve tissue. Solutions of procaine hydrochloride greater than 10 per cent should never be used for spinal anesthesia. Solutions of greater density than the spinal fluid are termed *hyperbaric solutions.* Those of a lesser density are called *hypobaric solutions. Isobaric solutions* are of the same density as the spinal fluid. Diluted solutions of the anesthetic agent result in shorter periods of anesthesia, less relaxation, and less possibility of nerve injury.

If the patient undergoing surgery under spinal anesthesia is apprehensive, unconsciousness may be achieved by the injection of thiopental sodium or the inhalation of nitrous oxide-oxygen mixtures.

Continuous spinal anesthesia has proved to be a satisfactory procedure for the administration of spinal anesthetics. It permits a smaller initial dosage of the agent and provides for the augmentation of the anesthesia as the relaxation diminishes and as the operative procedure requires. For this purpose a small flexible needle or catheter is left in place. It is connected to a syringe with a rubber tube of small diameter. Special equipment must be used (Lemmon, 1940).

**Continuous lumbar peridural anesthesia.** Peridural anesthesia involves the use of a *local anesthetic agent at some point along the spinal column paralyzing the nerve trunks and ramifications at or directly beyond their egress from the dura.* The agent does not enter the spinal canal. It appears to reduce the hazard of nerve damage. The nerve trunks at the point of egress from the dura have acquired protective sheaths of *endoneurium, epineurium,* and *perineurium.* The onset of anesthesia is therefore slower.

Hingson (1944) described a method of giving continuous peridural anesthesia by the use of a malleable needle. The procedure was later modified by the use of a Tuohy needle and a ureteral catheter. There are many modifications of the method adapting it to obstetrical, surgical, and therapeutic nerve-block procedures.

**Caudal anesthesia.** The peridural space can be approached for the purpose of producing anesthesia from the sacral canal. This type of spinal anesthesia has been referred to as *extradural sacral* or *caudal block.* The sacral hiatus is located. An 8-cm. needle is introduced at a 20° angle to the plane of the back. After piercing the tough ligament, it is horizontally directed, parallel to the back, until about 5 cm. of the needle has been inserted into the sacral canal. A solution of 2 per cent procaine hydrochloride (25 to 30 ml.) is instilled into the canal. This is sufficient for operations on the bladder, rectum, genitalia, and perineum.

Caudal block has been used successfully in mitigating labor pains. It has also been used for suprapubic prostatectomy.

*Fractional caudal anesthesia* can be provided by using a 13-gauge needle for the initial insertion into the caudal canal. A ureteral catheter is passed through the needle into the canal and the needle is then withdrawn (Adams, 1944). The fractional caudal block is used chiefly in obstetrics. Its advantage is similar to that of continuous spinal anesthesia, also used in obstetrics; namely, it permits a greater flexibility in dosage schedule.

**Saddle block anesthesia.** Saddle block anesthesia is so called because the regions anesthetized correspond to the parts of a horseback rider which are in contact with the saddle. It is a *low dosage hyperbaric spinal anesthesia* and is very popular in the United States today. By the addition of glucose to the spinal anesthetic agent, localization and concentration of the drug in the conus of the dural sac are facilitated. With procaine hydrochloride from 35 to 50 mg. are employed in a small volume of 10 per cent glucose solution. This method of anesthesia was described first by Adriani in 1946, and has been used extensively to abolish pain of delivery and subsequent procedures.

**Postspinal anesthetic sequelae.** Headache occurs in about 30 per cent of the patients subjected to spinal anesthesia. It is more frequent in women than in men. The pain is aggravated by sitting up and mitigated by the patient's assuming the Trendelenberg position. The precise cause of the headache is not clearly understood. Headaches may occur after simple lumbar puncture. The intrathecal pressure is sometimes lower during the period of headache. If this is the case, relief can be afforded by the intrathecal injection of warm saline solution (Pickering, 1939).

Krueger *et al.* (1951) believe that many postspinal headaches are caused by leakage of cerebrospinal fluid through the dural puncture hole.

If the rate of loss exceeds the rate of formation, headache is likely to follow. They recommend smaller needles; also inserting the beveled needle parallel to the dural fibers is helpful. Keeping the patient recumbent and well hydrated has had a salutary effect.

Joseph and Denson (1958) demonstrated that a source of arachnoiditis and paraplegia as sequelae to spinal anesthesia is the presence of strong detergent agents in syringes and needles as contaminants. Using a solution of trisodium phosphate as a detergent and inadequately removing the agent before autoclaving gave rise to arachnoiditis in 7 of 9 monkeys that were subjected to spinal anesthesia using these syringes. One monkey was clinically paraplegic. Thus it is clear that detergents as well as all other possible contaminants should be meticulously avoided when injecting a spinal anesthetic agent into the subarachnoid space.

In a review of about 1000 cases of spinal anesthesia Vandam and Dripps (1956) observed an over-all incidence of headache occurring in 11 per cent of the patients. The oldest patients appeared less susceptible, and there was a higher incidence among female patients than among men. They hold the view that a decrease of cerebrospinal fluid pressure because of leakage is the principal cause of headache. They state, "Headache could be virtually eliminated by the employment of a 24-gauge needle."

The head-down position for some hours after the injection appears to be one of the best prophylactic measures against the occurrence of headache.

Urinary retention is usually transient. Cholinergic agents such as Urecholine are used to initiate urine flow.

Transient palsies, permanent paralysis, and vertebral arthritis have been occasionally reported following spinal anesthesia (Hewer, 1946). The pathologic pictures were all similar and consisted of *radiculitis, cauda equina syndrome, ascending myelitis, adhesive arachnoiditis, bulbar involvement, and evidence of meningo-encephalitis.* These accidents are rare and are usually the result of faulty technic, poor choice of anesthetic agent, overdosage, or the careless postanesthetic management of the patient.

Dripps and Vandam (1954) obtained information on 89 per cent of more than 10,000 patients who have received spinal anesthesia. Their follow-up covered a period of 6 months, and patients with symptoms were followed longer. Headache was noted in 9 per cent of the males and 15 per cent of the females. Numbness or tingling in the feet, legs, thighs, or perineum occurred in 0.7 per cent of these cases. Leg cramps, pulling or drawing or twitching were experienced by 0.9 per cent of the group. Unilateral foot drop was observed in 2 patients of this series. All patients improved within 3 to 18 months. Unrecognized pre-existing neurologic disease which was present in 9 patients appeared to be aggravated by the spinal block. These data clearly indicate that if the procedure of spinal anesthesia is carefully carried out, severe neurologic damage need not occur, and minor complications are usually transient. This controlled study also points to the fact that neurologic symptoms as a rule do not develop after a latent period but are manifested shortly after the anesthetic block.

It now appears that many of the former disconcerting and often serious sequelae of spinal anesthesia have been due in a great measure to faulty technic and improper care of the patient after the anesthesia. Meticulous technic and the proper handling of the patient have been responsible for the reduction of the incidence of postspinal anesthetic problems to a minimum in recent years. Anderson cogently commented, "Spinal anesthesia is a method with great merit, but like many fine and delicate things, it must be handled with care."

**Therapeutic uses of spinal anesthesia.** Spinal anesthesia has been used in the treatment of peripheral arterial embolism of the lower legs. The vasodilation produced may cause the embolism to move further through the vessel and thus avoid operation. If this does not occur, the operation may be performed under the spinal block.

Other conditions in which spinal block has been used with limited degrees of success are eclampsia, cardiospasm, kidney blockage due to renal calculi, peripheral vascular pain, and hypertension tests prior to cervical sympathectomy.

**The future of anesthesiology.** Anesthesiology has now emerged into a distinct medical specialty. In recent years the production of new anesthetic agents and adjuncts to anesthesia have solved many of the former problems of the field. Relaxation and the obliteration of consciousness have now been achieved with comparative safety to the patient. More, however, will be accomplished in the future as new agents are made available and better technics of administering these agents are devised.

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# 23

# *Central Nervous System Depressants. Opium and Its Alkaloids*

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**Historical introduction.** Opium is one of the oldest drugs used by man. The Papyrus Ebers mentions the power of opium to obtund pain. In the Odyssey, Homer speaks of opium having been received by Helen of Troy from the wife of the King of Egypt. The value of opium to assuage grief is stated by Homer as follows: "Whoso drink thereof, no tears flow down his cheeks, though his mother and father die and men slew his brother or dear son before him and his eyes beheld it."

Opium was mentioned by Theophrastus in the third century before Christ. Galen, the distinguished Greek physician and pharmacist, employed opium to relieve pain and in his writings magnified its virtues. Down through the civili-

TABLE 23-1

*Principal Alkaloids of Opium*

| Chemical Group | Percentage in Opium |
|---|---|
| 1. Phenanthrene: | |
| Morphine | 10 |
| Codeine | 0.5 |
| Thebaine | 0.2 |
| 2. Benzylisoquinoline: | |
| Papaverine | 1 |
| Narcotine | 6 |
| Narceine | 0.3 |
| Laudanosine | traces |

zations of ancient Egypt and China, through the dark ages in Europe to the Renaissance and to the present day, the picturesque story of the opium poppy spins a thread of intriguing interest to mankind.

Paracelsus carried a piece of opium in the pommel of his sword. He named the extractive preparation, tincture of opium, *laudanum* from the Latin *laudo, I praise.* Sydenham, the distinguished English physician of the seventeenth century, was called Doctor Opiatus because he prescribed opium so frequently. He declared, "Who would be callused enough to practice medicine without opium." On another occasion he exclaimed, "Medicine would be a one-armed man without opium."

Wars have been waged to gain control of the opium crop. Treaties between nations have been signed regarding the commerce in this drug. The rules for regulating commerce in opium laid down by the former League of Nations were kept in force by the opposing belligerent forces in World War II. The United Nations has taken up the task where the old League discontinued, and under the new supervision rigorous international enforcement is in operation today.

**The source of opium.** The word *opium* comes to us from the Greek word ὄπιον which means poppy juice. The U. S. Pharmacopeia defines opium as the "*air-dried milky exudation obtained by incising the unripe capsules of Papaver somniferum Linnè or its variety album De Candolle (Fam. Papaveraceae).*" *Opium in its normal air-dried condition yields not less than 9.5 per cent of anhydrous morphine.*

The opium poppy is an annual plant with a thick, branching, yellow root. The stem is 2 to 4 feet high. The flowers appear in February and March, and are few in number. They are large (3 to 7 inches in diameter) with petals which are white or yellow.

Three or 4 fruit capsules occur on each plant. Shortly after the flower falls the fruit capsule is incised with transverse or spiral incisions. This is done in the afternoon. The juice exudes and solidifies on the outer surface of the capsule. The next day it is brown and is scraped off by native workers. The dried juice known as *gum opium* is compressed in baskets for shipping.

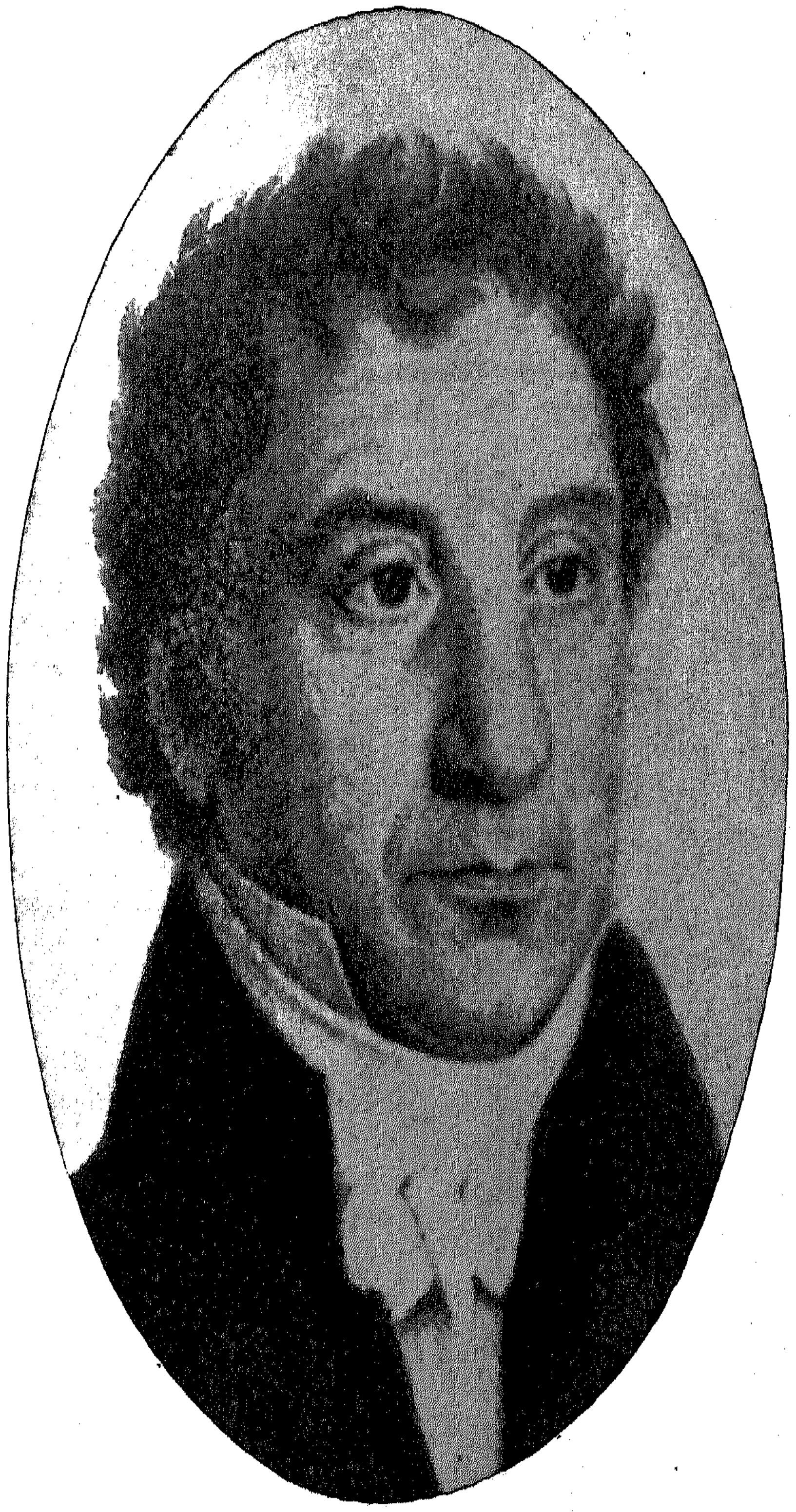
The opium poppy must be cultivated. The plant apparently requires rather rigidly controlled soil and climatic conditions. These are best met in Turkey, Iran, Egypt, and India. Most of the opium is cultivated in Asia Minor.

The United States produces no opium. All of the opium used in this country is imported. Some of it is used to make opium extractive preparations. Most of it is used as a source from which to extract morphine and the other alkaloids. Our imports of opium in 1963 were 245 metric tons: from this we made 734 kg. of morphine. Morphine manufacture has declined somewhat. However, the necessity for an increase in opium importation is entirely due to the fact that we have increased our manufacture of codeine to 26,637 kg. in 1963. It is interesting to observe how the use of meperidine, as a narcotic analgesic, has increased in the last decade and the use of morphine has declined. To illustrate, the average annual production of morphine in 1963 was 734 kg.; that of meperidine was 10,368 kg.

**The alkaloids of opium.** Friedrich W. A. Sertürner, an apothecary of Einbeck in Hanover, isolated morphine from opium in 1807. It was the first of all the vegetable alkaloids to be isolated. It was shown that most of the narcotic activity of opium was dependent upon the crystalline base morphine which Sertürner had separated from crude opium. The alkaloid was fittingly named "morphine" from the Greek god "Morpheus", the god of dreams. Opium contains many other alkaloids. The alkaloids of opium may be divided chemically into 2 groups, depending upon their structures. Table 23-1 shows this division.

In addition to the naturally occurring opium alkaloids there are several derivatives of morphine and codeine which are often referred to as synthetic opium alkaloids. Among these are heroin, dionin, and apomorphine.

The principal alkaloid of opium is morphine, and the pharmacopeias of most countries base



FRIEDRICH WILHELM ADAM SERTÜRNER
1784–1841

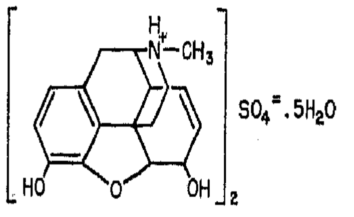
*The discoverer of morphine*

After taking morphine Sertürner exclaimed, "Now, fellow, watch out and tell me what happens, for this is of utmost importance to my experiment." (*From "Triumph Over Pain" by Rène Fülöp-Miller, copyright 1938. Used by special permission of the publishers. The Bobbs-Merrill Company.*)

the standard for opium upon its morphine content. Chemical assays for morphine in opium have been developed to a high state of reproducibility. They depend upon the selective extraction of morphine from opium with different solvents and the estimation of the crystalline base by virtue of its acid-consuming power.

**Chemotherapeutic considerations of morphine.** The structure of the morphine molecule has been definitely established. At long last in 1952 Gates and Tshudi of the University of Rochester succeeded in synthesizing morphine. Starting with Schaeffer's acid, a dye intermediate derived from coal tar, 27 different steps were necessary to achieve the synthesis of morphine.

Let us give consideration to the changes in the morphine molecule which have been responsible for the production of several useful synthetic alkaloids.



Morphine sulfate

It will be observed that morphine contains a phenolic hydroxyl group and also a secondary alcohol hydroxyl group. These are subject to esterification or alkylation with various substituent groups. Also the double bond between the 2 carbon atoms in the ring containing the secondary alcohol can be readily reduced. In addition, the secondary alcohol group can be oxidized to form a ketone in the ring. Furthermore, it should be noted that morphine contains a tertiary nitrogen atom which confers basic properties on the molecule. This makes possible the formation of the generally used salts of morphine: the sulfate; hydrochloride; and bitartrate.

By the replacement of the hydrogen atom of the phenolic hydroxyl group by a methyl radical, one obtains *methylmorphine* or *codeine.* This alkaloid is much less potent than morphine in its narcotic action. By the substitution of an ethyl group instead of a methyl group in this position, one obtains ethylmorphine or *dionin.* Its activity appears to be slightly greater than that of codeine.

By the replacement of both of the hydrogen atoms of the 2 hydroxyl groups in morphine by 2 methyl groups, and the introduction of a second double bond into one of the phenanthrene rings, the compound *thebaine* is obtained. Thebaine retains none of the narcotic action of morphine. Its action on the central nervous axis is stimulating. It produces convulsions. Thus one observes that the alkylation of these hydroxyl groups progressively diminishes the narcotic activity of the parent molecule, morphine.

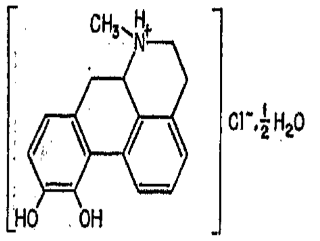
On the other hand, the esterification of the hydroxyl groups in the morphine molecule enhances its narcotic activity in general. By the acetylation of morphine one obtains *diacetylmorphine* or *heroin.* This synthetic alkaloid is approximately 5 times as potent as morphine.

If the secondary alcohol group in morphine is oxidized to a ketone and the double bond in the same ring reduced, one obtains *dihydromorphinone* or *Dilaudid.* This compound is about 5 times more potent than morphine and is claimed to have certain therapeutic advantages over the parent molecule.

By the introduction of a methyl group into the molecule of *dihydromorphinone*, replacing one of the hydrogen atoms attached to the carbon atom adjacent to the ketone group, *methyldihydromorphinone* or *Metopon* is formed. It appears to be twice as potent as morphine. Its analgesic action appears to last longer than its hypnotic effect.

By replacing the N-methyl group in morphine by an allyl group, N-allylmorphine or nalorphine is formed. This compound is a specific antagonist to the action of morphine and is used as an antidote in morphine poisoning.

When morphine is heated in a sealed tube with concentrated hydrochloric acid, it loses a molecule of water. The entire chemical constitution undergoes a change, forming *apomorphine.* The structure of apomorphine is shown in the accompanying formula.



Apomorphine hydrochloride

*Apomorphine* contains 2 phenolic hydroxyl groups, and furthermore the alkyl chain is shifted. This profound change in the arrangement of the atoms within the molecule increases the activity of the compound on the vomiting center. Apomorphine is used expressly for the purpose of producing emesis.

**The preparations of opium.** Since the isolation of morphine from opium there appears to be no necessity for the use of opium and its preparations. However, the use of these preparations in therapeutics continues. The two preparations of opium which are still used today are *opium tincture* or *laudanum* and *camphorated opium tincture*, or *paregoric.*

In former years laudanum and the aqueous extract of opium were used externally to relieve pain and allay itching. They were applied in lotions and ointments in the treatment of poison ivy affection, painful hemorrhoids, and other painful skin lesions. The evidence indicates that opium preparations exert no local anodyne effect, nor do they promote healing. Any beneficial results obtained by the use of opium locally were likely due to the absorption of the drug through broken skin and its subsequent action on the pain centers in the brain. The local application of opium is based upon a false premise and today must be considered beyond the pale of rational therapeutics.

The primary use of opium today is in the treatment of diarrhea. For this condition it was used by the Chinese centuries ago. The question arises whether it offers any advantage over morphine for this purpose. Morphine produces a spastic tonus of the sphincters of the gastrointestinal tract. Its over-all action is that of producing constipation. However, morphine produces a spastic tonicity of the intestines. The peristaltic waves initiated by morphine tend to combat the action of the drug on the sphincters. When opium is administered, which in addition to morphine contains the benzylisoquinoline alkaloids, the stimulating action of morphine on the gut is antagonized. These alkaloids are *antispasmodics.* Although their antagonism to morphine is marked on the course of the intestine, this does not obtain on the sphincters. This is illustrated by Zehbe (1913) in his studies of the passage of a bismuth meal in man. The normal passage was 26 hours. With 12 mg. of morphine the passage was delayed to 36 hours. However, with 1.3 ml. of tincture of opium the passage of the bismuth meal was delayed to 61 hours.

**Camphorated Opium Tincture, U.S.P. (paregoric)** represents 0.43 per cent of opium. It contains also 0.38 per cent of camphor, oil of anise, and benzoic acid respectively. This combined group of drugs has been used for years in the treatment of nonspecific diarrheas. After a cathartic has been administered to remove from the gut the offending intestinal contents, paregoric is then used to tranquilize the intestinal tract. Its dose is 4 to 8 ml. diluted in water. It is interesting to observe how this small concentration of opium is effective in checking diarrhea. The benzoic acid present is an antiferment. Camphor and oil of anise are carminatives.

In spite of the slight advantage offered by opium in the tranquilizing of the intestine, in the authors' opinion, it offers little that cannot be accomplished by morphine or codeine.

## THE PHARMACOLOGY OF MORPHINE

**Morphine on the brain.** The principal pharmacologic response of morphine is the *relief of pain.* Anesthetics accomplish this by producing a hiatus in consciousness and abolishing all motor activity. Morphine relieves pain without blocking motor activity and without seriously interfering with consciousness. Smith and Beecher (1959) studied the effect of morphine (10 mg./70 kg.) given subcutaneously to young healthy male students with placebo controls. Their sensations, moods, and feelings were determined by responding to suitable questionnaires. The most unpleasant and undesirable subjective responses recorded by the 61 individuals were mental clouding, physical inactivity, mental inactivity, and somatic responses such as dizziness, nausea, itching, headache, and feeling of warmth. The peak of effect occurred between one and 4 hours after medication. Some responses lasted, however, as long as 7 hours. They conclude that mental clouding and physical and mental inactivity are powerful effects evoked by morphine.

When morphine is administered to man the threshold to pain is apparently increased (Wolff *et al.*, 1940). Moderate pain will disappear. Sharp, piercing pain becomes dull and bearable. The pattern of one's reaction to pain changes; anxiety, vexation, and the alarm reaction to recurring pain are mitigated. These psychologic effects of morphine often last after the analgesia has disappeared. Morphine appears to be most useful in relieving pain arising from the viscera and trauma. Its use in arthralgias and integumental pain, although of value, does not compare with the dramatic results achieved with morphine in allaying visceral pain. Miller and Elliott (1955), using $C^{14}$-labeled morphine in rats, demonstrated that peak levels of the drug in the central nervous system correlated well with the pain-obtunding action of morphine.

During the period of morphine analgesia, sleep may be produced. This diminishes the sensitivity to pain also. Although the power of continuous attention is impaired, mental activity may readily be carried on under the influence of the drug. Light touch sensations carried over the posterior columns and the ventral spinothalamic tract are not appreciably impaired. Pain impulses carried over the lateral spinothalamic pathways may be completely blocked.

The depressant action of morphine (producing analgesia and hypnosis) appears to lie in the sensory area of the cerebral cortex. The excitant action which manifests itself in certain species, such as the cat and pig, seems to depend on the integrity of areas in the hypothalamus (Hambourger, 1940). Miller *et al.* (1955) presented evidence to show that morphine analgesia is not mediated by the release of epinephrine from the adrenal medulla. Adrenalectomy and adrenal demedullation did not decrease the pain reaction threshold of rats to morphine.

Andrews (1941) studied the effect of morphine on the human electroencephalogram. He concluded, after studying addicts and unaddicted individuals under the influence of the drug, as follows: "Addiction and not the drug *per se* is required to produce changes in the cortical potentials, for single doses produce little change in the electroencephalogram." The striking feature of the electroencephalogram of the addicted group of patients maintained by morphine dosage was the abnormally large amount of alpha activity as compared with normal individuals.

Morphine acts also on the medullary centers. The principal medullary centers affected by morphine are as follows:

1. Respiratory center—depressed
2. Cough center—depressed
3. Vomiting center—stimulated.

In most animals and in man, morphine depresses the centers of respiration, resulting in a decreased minute volume of gaseous exchange. The threshold to carbon dioxide stimulation is increased by morphine. The alveolar carbon dioxide tension is increased. The effects on the alkaline reserve of the blood are not regular. Sometimes there is an increase, and other times the reverse may occur. The effects on blood acidity are variable. The general shift is to the acid side and the degree about 0.05 pH unit (Krueger *et al.*, 1941).

In normal, healthy individuals respiration is slightly affected by a therapeutic dose of morphine. The minute volume usually diminishes from 10 to 15 per cent, and the oxygen consumption is decreased 8 to 10 per cent. The respiratory quotient is lowered.

Cohen and McGuigan (1924) proposed that the depression of the respiration by morphine has a peripheral component. This action of morphine is mediated through the blocking of afferent stimuli which would ordinarily stimulate the respiratory center. This is notably true when painful stimuli are present which would excite the respiratory center in the absence of the analgesia produced by morphine. The discomfort of dyspnea is frequently relieved by morphine owing to its capacity to raise the threshold of consciousness to painful or noxious stimuli.

Viewing the experimental evidence produced by various workers the preponderance of opinion indicates that the principal site of the *depressant action of morphine on the respiration is central.* When morphine kills, respiratory failure is the principal cause of death.

**Morphine and the cough center.** This center appears to be more sensitive to morphine than the centers of respiration. As a rule, 2 mg. of morphine will depress the cough center. It requires 10 to 15 mg. of morphine to depress the respiratory centers. Morphine is an excellent cough sedative and were it not for its addictive properties it would probably be the most useful drug in the treatment of the dry nonproductive cough. Its use, however, is confined to those cases where codeine and other antitussives have failed to give relief.

**Morphine and the vasomotor center.** Schmidt and Livingston (1933) produced evidence to show that stimulation of this center is not a prime factor in the depressor response to morphine. Actually, the depressant action of the drug on the vasomotor center plays only a minor role in its depressor response. The diminished vasomotor response to carbon dioxide inhalation produced by morphine appears to be a resultant of the respiratory depression of the drug. Therefore one must look to a peripheral component of the action of morphine to account for its depressor response and consider the effect *on the vasomotor center as only a minor contributing factor.*

**Morphine on the vomiting center.** The evidence is convincing that morphine *stimulates the vomiting center directly.* Hatcher and Weiss (1923) found that 1 μg. of morphine applied directly to the floor of the fourth ventricle produced the vomiting syndrome in dogs after the gastrointestinal tract had been removed from the cardia to the anus. These investigators held the view that morphine lowers the threshold of the vomiting center to make effective otherwise inadequate stimuli. Koppanyi's (1933) studies, on the other hand, indicate a direct emetic effect

of morphine. In either case the site is the medulla, and *the action is central.*

Borison and Wang (1953) showed that the emetic action of morphine is not due to direct stimulating action on the vomiting center in the medulla. The drug serves to stimulate the specialized chemoreceptor trigger zone in the surface of the medulla. Apomorphine, page 368, was shown by the same investigators to act upon this trigger zone mechanism.

The nausea and vomiting elicited by morphine appear to be far more frequent in ambulatory patients than in those who remain in bed. It is possible that the action also possesses a vestibular component. Rubin and Winston (1950) showed that nausea and emesis elicited by morphine are aggravated by vestibular stimulation.

**Morphine on the spinal cord.** The reflex centers of the spinal cord are stimulated by morphine. In the decerebrate frog small doses of morphine produce convulsive seizures. These frequently resemble the response of the frog to strychnine. With an intact central nervous axis larger doses of morphine are required. Further, the onset of the convulsion is delayed. Apparently the depressant action of the drug on the higher centers in the brain antagonizes the hyperreflexia which it produces on the spinal cord. The action of morphine on the spinal cord producing reflex excitability interdicts the use of the drug in strychnine tetany.

**Morphine on the pupil.** Morphine produces a *pinpoint constriction* of the pupil. So constant has been this observation in man that it is considered to be diagnostic. The rabbit and dog show pupillary contraction, the cat shows dilatation, and birds' pupils are not affected by morphine. The mechanism of the myosis of morphine is complicated. The literature reports are not in agreement. Nor is there adequate explanation for the wide species variations.

The consensus indicates that the *action of morphine on the pupil is central.* The following experiments support this view.

1. Direct application of 0.1 per cent morphine solution to the cerebrum of rabbits caused myosis (Kinukawa, 1933).
2. Instillation of morphine solution 0.5 per cent into the conjunctival sac did not produce myosis.
3. Sectioning of the cervical sympathetic nerve did not affect the myosis.
4. Sectioning of the oculomotor nerve unilaterally obliterated the myotic response to morphine. The pupil with the intact innervation still showed myosis.
5. Morphine produced no myosis in the decerebrate rabbit.

It is therefore concluded that the myosis of morphine results from its cerebral effect. This effect is mediated through a greater tone of the oculomotor nerve which innervates the sphincter muscle of the iris.

It has been stated that when morphine solutions are instilled into the conjunctival sac, myosis does not occur. Morphine, however, stimulates the radial and circular muscles of the iris. These effects are compensatory. Simultaneously, it stimulates the ciliary muscle and fixes the eye for near vision. This is observed in the atropinized pupil, in which morphine produces a spasm of accommodation.

As tolerance for morphine in the cerebral centers is developed by repeated dosage, the pupil does not share this tolerance. *The addict continues to show myosis.*

**Morphine on the autonomic nervous system.** There is convincing evidence to show that morphine enhances parasympathetic activity. It has been stated that morphine constricts the pupil centrally; this action is mediated through the oculomotor nerve. Morphine also inactivates cholinesterase, which synergizes the action of parasympathomimetic drugs. Its action on the gastrointestinal tract is likewise suggestive of parasympathetic activity. The action of morphine in inactivating cholinesterase has suggested that morphine is capable of producing stimulation of both types of postganglionic fibers by its action at the synapses. Morphine often produces hyperglycemia. This may be due to the release of catecholamines. Adrenalectomized rabbits are much less resistant to the action of morphine than normal animals (Anton, 1931).

**Morphine on the circulation.** The effect of morphine in therapeutic doses on the circulation is not marked. This statement holds for man and the usual experimental animals. In the study of morphine on the brain it was stated that morphine mildly depresses the vasomotor center. This plays a minor part in the depressor response evoked by the drug. Perfused hearts of dogs, guinea pigs, cats, and rabbits are first stimulated by the presence of morphine. The hearts are then depressed in rate and force of beat. Irregularities, heart-block, and finally diastolic arrest occur. The effective concentration is between 1:20,000 and 1:10,000.

In the intact dog, when intravenous injections of morphine were given 1 mg./kg., at the peak of the depressor response, the myocardiograph showed no significant diminution in the strength or output of the heart. The depressor effect therefore appears to be on the *peripheral circulation* (Schmidt and Livingston, 1933).

The direct action of morphine on the blood vessels of the abdominal viscera is essentially constricting. The action on the vessels in the skin and muscle is dilator in character. Hence the two peripheral effects on the smooth muscle of the blood vessels are compensatory. One must look then to the capillaries for the site of dilatation. The response of the leg volume of the cat and dog to small intravenous doses of morphine resembles that of histamine. Indeed, morphine often evokes itching of the skin, especially the nose, which is likely due to the release of histamine. This leads one to the opinion that the site of the *depressor response of morphine is in the capillary bed.*

The *coronary vessels are dilated* when perfused with morphine solutions. In the intact dog 5 to 6 mg./kg. of morphine injected intravenously prevented for more than an hour the coronary constriction produced by posterior pituitary injections in normal animals (Mautner and Pick, 1929).

McCall and Taylor (1952) studied the effects of morphine in 7 normal and 12 toxemic pregnant women. Various facets of respiratory metabolism and respiration were explored. Their significant findings were a slight lowering of the blood pressure and a concomitant increase in cerebral blood flow. They conclude that the response to morphine in their patients appeared to be "more physiologic" than that of intravenous barbiturate medication.

Much (1929) showed that morphine accelerates the coagulation of blood. He suggested that morphine acted like a *kinase.* When added to citrated rabbit's plasma it caused the formation of a clot. In rabbit's blood Ri (1937) observed that the time for complete clotting was diminished by 50 per cent by the presence of 1 per cent of morphine.

**Morphine on the bronchioles.** Therapeutic doses of morphine *do not cause constriction of the bronchioles in man.* Large doses in laboratory animals elicit bronchiolar constriction. In patients with asthma, the possibility of morphine's causing further bronchiolar constriction should enjoin one with caution in its use in this condition.

**Morphine on the urinary tract.** Morphine produces a spasm of the vesical sphincter which tends to check urinary flow. This, however, is antagonized by an increase in tone of the detrusor muscle of the urinary bladder. Morphine appears also to exert an antidiuretic action mediated through the posterior lobe of the pituitary. The over-all effect is one of urinary retention.

**Morphine on the biliary tract.** Morphine increases biliary pressure in man. Biliary spasm may also be produced by morphine. The spasm is not antagonized by atropine but does respond favorably to the inhalation of amyl or octyl nitrites. Smith *et al.* (1952) demonstrated that an injection of morphine may cause as much as a 10-fold increase in pressure in the biliary tract. The effect occurs within 5 minutes after the injection, reaches its peak in 15 minutes, and may continue for as long as 2 hours. It is therefore evident that the relief of pain which morphine evokes in biliary spasm is *not due to its action on the biliary tract, but is sequential to its analgesic action.*

**Morphine on the gastrointestinal tract.** It has been previously shown that the over-all effect of *morphine on the gastrointestinal tract in man is constipative.* There is a delayed emptying time of the stomach. This is caused by the contraction of the pyloric sphincter, and to a lesser extent by diminished gastric motility. Paton (1957) showed that morphine inhibits the release of acetylcholine in the postganglionic structures of the intestine. The effective propulsive movements of the small intestine are diminished by morphine. The tone is increased, and nonpropulsive movements may also increase in number, resulting in spasm. The tone of the ileocecal valve is increased by morphine, further delaying the passage of the bolus to the colon. The effect of morphine on the colon is similar to its action on the small intestine. Propulsive peristaltic movements are diminished or even obliterated, and the colon enters a state of spastic tonus, aggravating constipation. The tone of the anal sphincter is augmented, and further, the lack of perception of the individual to the usual sensory stimuli which precede a bowel movement contributes further to the constipating action of the drug. The main constipative action of morphine on the gastrointestinal tract is a direct musculotropic effect.

Green (1959) studied the action of morphine and other narcotic analgesics on pain threshold, respiratory frequency, and gastrointestinal propulsion using a charcoal meal in the rat. He found the ratio of the analgesic dose to the dose preventing the transport of the charcoal meal about the same for morphine, meperidine, methadone, codeine, and other narcotic analgesics. When administered in moderate analgesic doses, morphine appeared to evoke a greater constipative effect than meperidine. When morphine was administered intracisternally to rats, the effects on the spinal reflex of the tail were dissociated to some extent from the action on the threshold for a squeak response. The respiratory depression paralleled the delaying of the transport of the charcoal meal. Green considers this further evidence that the action of morphine on the gastrointestinal tract comprises a central component. The delay of the transport of the charcoal meal elicited by morphine was diminished by nalorphine.

Gray (1958) observed that the gastrointestinal action of morphine and certain other analgesics was antagonized by nalorphine and levallorphan in trained unanesthetized dogs. The antagonism studies failed to reveal a constant analgesic-to-antagonist ratio. On the other hand, the absolute dose of antagonist required for the initial prevention or reversal of analgesic-induced hypertonicity of the gut, remained remarkably constant regardless of the analgesic over a 100-fold dosage range.

The action of morphine on the enzymes of the gastrointestinal tract is not marked. In man, gastric secretion is diminished from 10 to 20 per cent (Wang *et al.*, 1936).

**Morphine on metabolism.** The presence of morphine in the blood exerts an effect on the metabolic pattern of the individual. Most phases of metabolism are influenced. Carbohydrate metabolism is affected in all species studied including man. Morphine produces a transient hyperglycemia in man. Reducing substances are often found in the urine. Glucose, acetone, and lactic acid have been identified.

The hyperglycemia of morphine appears to be the resultant of the mobilization of liver glycogen and other glycogen stores. The effect on the liver is probably mediated through epinephrine release and the stimulation of the sympathetic glycogenolytic fibers. There may be, however, a pancreatic component involved. In dogs the denervation of the pancreas increases the hyperglycemia. In the absence of abdominal sympathetic innervation morphine produces a slight hypoglycemia in the dog which disappears upon vagotomy. It appears, however, that the primary cause of the hyperglycemia is through a sympathetic discharge to the adrenals and through this mechanism mobilizing liver glycogen. The repeated administration of morphine in man appears to disturb carbohydrate fixation in the liver. Urobilinogen may occur in the urine.

Unequivocal evidence for disturbance of nitrogen balance caused by therapeutic doses of morphine is not to be found. The same appears to obtain for fat metabolism.

Data on the effect of morphine on mineral metabolism are fragmentary and often contradictory. There appears to be some evidence that the calcium content of the blood slightly increases, and the inorganic phosphates of the blood diminish in man after therapeutic doses of morphine. The magnitude of the changes is small and not of therapeutic significance.

McDonald *et al.* (1959) demonstrated that therapeutic doses of morphine affect the hydrocortisone levels of normal persons. The action was one of suppressing the hydrocortisone level, which was interpreted by the investigators as a suppression of the early morning release of adenocorticotrophic hormone (ACTH) in sedated individuals. In nonsedated subjects morphine was shown to be capable of depressing mid-day ACTH release as well as that induced by a standardized stress produced by vasopressin. The adrenals were shown to be normally responsive to injected ACTH after the administration of morphine.

Eisenman *et al.* (1958) showed that doses of 45 mg. of morphine sulfate given to male subjects caused a decrease in excretion of urinary 17-ketosteroids. Addiction to morphine was accompanied by decreased excretion of 17-ketosteroids. Partial tolerance to this effect of morphine developed with long periods of addiction (143 days). Striking rises in the excretion of urinary 17-ketosteroids occurred with withdrawal of the drug and the level of excretion usually exceeded the predrug level. These investigators observed, as did McDonald *et al.* (1959), that the adrenal cortex was sensitive to the injection of ACTH after morphine administration, even during the addiction period.

Morphine exhibits an effect on water balance. In the pre-insulin days morphine was used in the treatment of diabetes. The volume of urine excreted was reduced, but a marked oliguria was seldom produced. In certain disease conditions morphine may produce a diuresis. This has been observed in puerperal eclampsia and in cardiac patients under digitalis therapy (Krueger *et al.*, 1941). The routine use of morphine does not influence the kidney as shown by the phenolsulfonphthalein output. It is therefore not interdicted in kidney disease.

DeBodo (1944) destroyed the neurohypophysis and produced permanent diabetes insipidus in dogs. Upon the administration of 5 mg./kg. of morphine the polydipsia and polyuria were checked for a period of 9 hours. Although it is doubtful that this experiment has clinical application since the disease is adequately controlled by pituitary solution, it is further evidence that morphine does affect water balance.

George and Way (1959) showed that lesions of the hypothalamus in rats which produced diabetes insipidus blocked the antidiuretic effect of small doses of morphine (0.1 mg./kg.), but failed to inhibit the response to larger doses (1 to 10 mg./kg.).

Crawford and Pinkham (1955) demonstrated on rats that the antidiuretic action of morphine involves 2 components. The first consists of a reduction in the rate of urine formation, involving no change in the ratio of water to total solids. The same result is achieved by constricting the renal artery. They interpret this change as the response to changes in renal hemodynamics elicited by morphine. The second component in the antidiuretic action is manifested only in the presence of the preformed antidiuretic hormone. Morphine enhances the action of the hormone. This antidiuretic action is characterized by a reduction in urinary water output with no change in the excretion rate of total urinary solutes. Thus morphine does not appear to stimulate the release of the antidiuretic hormone, but on the other hand augments its action.

Schnieden and Blackmore (1955) showed that the antidiuretic action of morphine in the rat was diminished by a simultaneous injection of nalorphine, which alone produced no antidiuretic action. In man, to whom water was given, nalorphine evoked antidiuresis in some individuals. Morphine produced an antidiuretic action in man which was not abolished by the simultaneous injection of nalorphine.

Shideman and Seevers (1942) fed rats an adequate diet and simultaneously chronically poisoned the animals with morphine over 8 weeks. These animals showed a mean increase in weight of 50 per cent contrasted with a 93 per cent gain in a control group. Of special interest is the fact that oxygen consumption of skeletal muscle of the morphinized rats was 44 per cent greater than that of the controls. This is confirmatory of former work that morphine definitely stimulates aerobic metabolism of skeletal muscle.

**The absorption, fate, and excretion of morphine.** In man, morphine can enter the general circulation by any of the usual pathways. Some absorption may occur from the stomach upon oral administration. It is readily absorbed from the small intestine. It is absorbed promptly from the sites of subcutaneous injection of solutions of its salts.

When morphine is absorbed the organism begins at once to excrete the drug in the urine and feces. Man eliminates about ⅙ of the drug in the excreta. In small quantities it is present in the saliva and perspiration. It may be present also in milk. The liver is capable of destroying morphine. Seevers *et al.* (1952) showed that liver tissue slices incubated with morphine caused a 38 per cent disappearance of the alkaloid. Under the same conditions kidney tissue caused a 5 per cent loss of morphine. Brain and skeletal muscle did not cause a significant loss of the drug.

Studies in man, using $C^{14}$-tagged morphine, have elucidated its fate in the body. Elliott *et al.* (1954) injected morphine into 4 normal individuals and 1 addict and found that most of the radioactivity was excreted during the first 24 hours. Urinary excretion accounted for about 90 per cent of the radioactive recovery; the feces for 7 to 10 per cent. Pulmonary excretion in $C^{14}O_2$ accounted for a small percentage of the excretion (3.5 to 6 per cent). There were no sex differences observed in man, as prevails in the rat. The addict pattern of excretion of morphine was similar to that of nontolerant individuals except for the appearance of only a trace of radioactivity in the feces (0.1 per cent).

Oberst (1942) observed that a large percentage of the morphine excreted in the urine is in a conjugated form. It appears that the phenolic hydroxyl group is involved in the process of conjugation, and the product is the glucuronide (Cochin *et al.*, 1954). It is freed by treatment with hydrochloric acid. By this treatment of the urine, Oberst found that the average total excretion of morphine in the urine is 30.5 per cent of the intake. Of this only 5 per cent was free morphine. The percentage output of morphine, free and bound, appeared to remain the same irrespective of the intake. The excreted morphine is expressed in percentage of total intake. The percentage of free morphine excreted after subcutaneous injection is more than double that which occurs when the drug is given orally. Seevers *et al.* (1952) showed that the total excretion of morphine in the nontolerant dog was the same whether the drug was administered parenterally or orally. Parenteral administration accelerates the initial rate of excretion.

Woods (1954) extensively investigated the distribution of morphine in rats and dogs. His conclusion is of interest and conforms with the observation of Elliott *et al.* (1954) concerning the fate of morphine in man. Woods asserts, "No acceptable evidence has been presented here, or elsewhere, to support the view that altered distribution or fate of morphine is associated with, or responsible for, tolerance development or physical dependence."

**The toxicity of morphine.** It is difficult to set a toxic dose for morphine. Ordinarily 200 mg. is considered a fatal dose. Whether recovery or death will follow the administration of an overdose of morphine depends upon a great number of factors. The aged and cachectic persons are particularly vulnerable to the drug. In addition, infants are especially susceptible to morphine and most of its derivatives.

The person poisoned with morphine is at first depressed. The pupils are constricted. The peripheral vasodilatation of the therapeutic dose of morphine with its concomitant flushing is replaced by pallor and cyanosis. The respiration is slow, and coma becomes profound. The respiration ultimately changes to the Cheyne-Stokes type. The pulse is slow and weakens in force; then the heart becomes irregular. If the dose of morphine is large, convulsions may occur just prior to death. Death comes slowly. There is time in which to act. Generally death occurs 5 to 10 hours after the giving of the drug. Patients who survive for more than 10 hours recover from the intoxication as a rule.

It has been considered by most authors that morphine causes death entirely by asphyxia. Undoubtedly this plays an important role. Nevertheless the circulatory component of the intoxication must also be given considerable weight. Kipp (1904) reported 6 cases of morphine poisoning all of which, according to this observer, died of cardiac failure. He stated, "All were breathing at a rate of 16 to 18 a minute, and doing fairly well when there occurred a sudden cardiac acceleration and subsequent stoppage."

Schmidt (1924) made a study of various respiratory stimulants to combat the depressed respiration produced by morphine and heroin. He commented,

> "A study of the clinical records of patients with morphine or opium poisoning in this hospital showed that wherever observations were made of the circulation on patients in a critical condition, there were signs of serious circulatory depression, and as the condition improved under treatment the circulation also improved. One patient died of morphine poisoning, and the pulse could not be felt 10 minutes before respiratory failure; pulmonary edema was present, for which the autopsy showed no organic or infectious cause, so that it may have been due to extreme circulatory depression. It is possible that circulatory depression plays a greater part in the dangers of morphine poisoning than is generally realized."

**Treatment of morphine poisoning.** In 1883 Stearns wrote, "Let the physician remember that the real antidote to opium is pain, and as far as known, there is no other." We have retained Stearns' antidote through the years and added others that are helpful in effecting recovery.

N-allylnormorphine hydrochloride (Nalline) has become the most generally used antagonist to the respiratory depressant effect of morphine. It is given in 5- to 10-mg. doses intravenously or subcutaneously and may be frequently repeated (Eckenhoff *et al.*, 1952). The action of this agent is discussed on page 369. This is the drug of choice to combat the respiratory depressant effects of morphine.

Amphetamine sulfate, 15 to 25 mg., subcutaneously is a powerful antagonist to the respiratory and circulatory depression of morphine poisoning.

The old antidote of Stearns should not be neglected. Keep the patient walking around supported by attendants. Faradic shock, flicking with towels and any source of peripheral pain are valuable in combatting coma.

If the opiate has been administered orally, gastric lavage should be instituted. The stomach may be washed with a claret-colored potassium-permanganate solution (0.2 gm. to 500 ml.). This oxidizing agent detoxifies morphine. Tannin-bearing extracts such as strong tea and adsorbents like animal charcoal may be found helpful. Exchange transfusion should also be considered.

**The therapeutic uses of morphine.**

1. The principal therapeutic use of morphine is to relieve severe pain.
2. Morphine is useful in checking diarrhea.
3. Morphine is valuable in the treatment of dry, nonproductive coughs that have failed to yield to codeine.
4. Morphine is used for pre-operative medication.
5. Morphine is indicated in surgical hemorrhage. The blood pressure is reduced, and bleeding diminishes.
6. Morphine is useful as a hypnotic when severe pain interferes with the ability to sleep, after hypnotics which are potentially less harmful have failed to induce sleep.

Traditionally the therapeutic dose of morphine salts is 15 mg. Lasagna and Beecher (1954) carried out an extensive study to determine if 15 mg. is the optimal dose, *i.e.*, for desired relief of pain with minimal side effects. They found that when administered to 122 patients post-operatively there was only a slight increase in potency and duration when the dose was increased from 10 to 15 mg. In normal volunteers 15 mg. produced more respiratory depression and a higher incidence of troublesome side effects than did 10 mg. of the drug. They believe that the optimal dose of morphine routinely is 8 to 10 mg. It appears that, since side effects and addiction are hazards of morphine therapy, the smallest effective dose should be employed first.

Christie *et al.* (1958) studied a series of volunteers receiving morphine up to 30 mg. with regard to untoward side effects. In their series of 46 persons, the most frequent side effect was nausea and vomiting. This was encountered in about $\frac{1}{8}$ of the subjects. The onset of emesis may be delayed for as long as 7 hours. This side effect was completely controlled by the use of cyclizine hydrochloride 50 mg. Central nervous system depression was controlled by the administration of 50 mg. of amiphenazole. They hold the view, that since effective antidotal drugs are available to control the side effects of morphine, the patient with chronic pain should not be denied the complete analgesia afforded by large doses of morphine.

In all of the therapeutic uses of morphine one should be cautioned against the capacity of morphine to mask the underlying causative factors in the illness. Thus, in the pain of biliary colic, it brings relief by its central action but actually may aggravate the condition. It should be repeated here for emphasis that morphine depresses the respiration and is capable of producing circulatory collapse. *The greatest drawback to the use of the drug, however, is the danger of addiction.*

The most generally used avenue of administration for morphine is by subcutaneous injection. It may be given orally also. During World War II the intravenous use of morphine increased. Except in excruciating and unbearable pain as an emergency measure, intravenous morphine does not appear to be necessary.

### MORPHINE DERIVATIVES

**Codeine Phosphate, U.S.P.** Codeine is present in opium to the extent of about 0.5 per cent. The word in Greek means the head of the poppy. Most of the codeine is made from morphine by methylation. It is methylmorphine. For many years the sulfate of codeine was the salt that was preferred. It is soluble in 30 parts of water. More recently the phosphate of codeine has gained in popularity. It is soluble in 2.3 parts of water. *Codeine phosphate* is the salt of choice.

Codeine is one of the most frequently prescribed drugs. It has a wide field of usefulness in clinical medicine. It owes this largely to the fact that it depresses the cough center. On the cough center its activity vies with that of morphine. On the higher centers in the brain, however, the action of codeine is approximately $\frac{1}{10}$ that of morphine. Thus it appears to be the drug of first selection in the treatment of cough.

The diminished effect of codeine on the cerebral centers is manifested in at least 2 ways. First, codeine does not as a rule produce a euphoria, and hence addictive possibilities are slight. Second, as an analgesic codeine is far inferior to morphine. Even its generally accepted maximal dose of 60 mg. cannot vie with 10 mg. morphine in its capacity to obtund pain.

Houde and Wallenstein (1953) compared the analgesic action of codeine and morphine in treating patients with chronic pain. They found that the time-effect curves in patients receiving 11 mg. of morphine intramuscularly were of about the same configuration as those receiving 82 mg. of codeine by the same route. The peak effect was achieved in about 1 hour and the duration approximately 6 hours. Even at this dosage difference the mean pain relief achieved with morphine was slightly greater and of somewhat longer duration than that accomplished by codeine.

Individuals with arthralgic pain used codeine as an analgesic for years without showing tolerance or addiction, although there have been reported cases of codeine addiction, and others have recognized tolerance.

Codeine is readily absorbed from the gastrointestinal tract and from the subcutaneous tissues. It may also be given intravenously. Adler *et al.* (1955), using $C^{14}$-tagged codeine, studied the fate of the alkaloid in man. Following an injection of 30 mg. only, negligible quantities of $C^{14}$ were found in the feces. The major fraction was found in urine within 24 hours in the products of codeine metabolism. These were identified as 1.2 to 4 mg. of morphine, 2.2 to 2.8 mg. of norcodeine, and 10.7 to 11.7 mg. of bound codeine. The amounts of unaltered codeine varied from 1.5 to 3.7 mg. Upon oral administration there was no marked difference in the biotransformation of codeine. About half of the dose was excreted within the first 6 hours after administration. It was shown that in the biotransformation of codeine both methyl groups can be removed from the molecule, the N-$CH_3$ yielding norcodeine and the $OCH_3$ yielding morphine.

*Codeine is employed principally in the relief of cough.* Its untoward effects are constipation (similar to morphine) and in some individuals it produces *xerostomia.* Its second use is to allay pain which does not respond to the milder analgesics, acetylsalicylic acid, and similar drugs. It is a hypnotic. With severe cough, however, the combination of codeine and a barbiturate appears to be superior to the dependence upon codeine as a hypnotic alone.

TABLE 23-2

*Nonaddictive Antitussives*

| Generic Name | Trade Name | Average Adult Dose |
|---|---|---|
| | | *mg.* |
| Dextromephorphan hydrobromide | Romilar | 10 to 20 |
| Carbetapentane citrate | Toclase | 15 to 30 |
| Noscapine (narcotine) | Nectadon | 15 to 30 |
| Benzonatate | Tessalon | 100 to 200 |
| L-Propoxyphene | Novrad | 50 to 100 |
| Dimethoxanate | Cothera | 25 to 50 |

Codeine is often prescribed for cough in the form of Terpin Hydrate and Codeine Elixir N.F. (dose 4 to 8 ml.) containing 8 to 15 mg. of codeine.

### NONADDICTIVE ANTITUSSIVES

For more than a decade The National Research Council's committee on Drug Addiction and Narcotics has encouraged the synthesis of nonaddictive analgesics. The program has produced results in the appearance of several new drugs which are not addictive and are effective as antitussives. The work has been facilitated by the use of quantitative screening procedures for antitussive activity in laboratory animals and man. One of the most generally used screening methods is the suppression of the experimental cough evoked in man by citric acid aerosols. A list of several of these nonaddictive antitussives is shown in table 23-2.

**Dextromephorphan Hydrobromide; Romilar** is another nonaddictive antitussive agent that enjoys rather wide use. Chemically Romilar is *dextro-3-methoxy-N-methylmorphinan hydrobromide.* Pharmacologically the compound was studied by Benson *et al.* (1953). In animal experiments it was shown that Romilar suppressed cough without inducing *sleep*, *ataxia*, or *lethargy.* Romilar was found to stimulate respiratory activity in the rabbit. Romilar increased the threshold to experimentally induced cough in cats by its central action. The frequency of cough was diminished but the amplitude remained unaffected. Of special interest is the fact that at doses of 5 mg./kg. ciliary activity was not diminished. Isbell and Fraser (1953) determined that Romilar was devoid of addiction liability.

Cass and Frederik (1953) studied Romilar clinically in 183 cases and concluded that Romilar was as effective an antitussive as codeine and free from side effects. Ralph (1954) extensively investigated Romilar as an antitussive and concluded that on a weight basis Romilar was twice as effective as codeine. Further, they found that side effects were rare, consisting of dizziness in one patient and nausea in another in a series of 183 cases.

The onset of antitussive action occurs in 15 to 30 minutes after administration, and the duration is from 3 to 6 hours. Romilar is available in 10-mg. tablets (1 to 4 tablets daily) and as a syrup containing 10 mg. in a teaspoonful.

The incidence of side effects with Romilar has been low and it appears that in a segment of patients with cough, it compares favorably with codeine. A special virtue of Romilar is the absence of constipative action.

**Noscapine N.F. (Nectadon, Narcotine).** Narcotine is one of the benzylisoquinoline alkaloids found in opium. It is nonaddictive and elicits no analgesic action. Winter and Flataker (1952) showed that narcotine evoked antitussive activity in laboratory animals. Bickerman and Barach (1954) demonstrated the antitussive action of narcotine in man. The activity was equal to that of codeine. Narcotine appears to elicit minimal side effects and tolerance does not develop. Narcotine is especially useful in the treatment of spasmodic cough. Dose response curves in cough suppression with narcotine showed additive effect with increasing dosage with a duration as long as 6 to 8 hours. The recommended dose of narcotine is 15 to 30 mg., as high as 90 mg. were administered daily for 4 to 6 weeks and well tolerated as observed by Bickerman and Barach. It will be interesting to observe whether or not this alkaloid of opium which has lain almost dormant therapeutically since 1821 will warrant a definitive place in the armamentarium as an antitussive.

**Benzonatate (Tessalon).** Tessalon is an antitussive agent which is chemically related to the local anesthetic tetracaine. Chemically it is ω-methoxypoly(ethyleneoxy)ethyl *p*-butylamino benzoate. It occurs as a viscous liquid and is administered in capsules.

The action of Tessalon upon the cough center is not entirely central, but the drug evokes a high degree of specificity toward the sensory receptors of the vagal afferent fibers involved in cough production. It is suggested that after absorption, the compound elicits its anesthetic action on these structures, tantamount to the topical application of a local anesthetic agent to the respiratory mucosa.

Tessalon also evokes a central action by inhibiting the transmission of impulses of the cough reflex in the vagal nuclei. It also depresses polysynaptic spinal reflexes. The comparative value of the central and peripheral actions of Tessalon in cough suppression has not been established.

Tessalon was found to be as effective as codeine in the suppression of experimental cough in animals and man. In cough associated with various illnesses, the efficacy of Tessalon is somewhat less impressive. Tessalon has been found to be especially useful in suppressing coughs associated with chronic bronchitis, pulmonary tuberculosis, advanced emphysema and bronchial asthma. It is also of value in bronchoscopy. In a group of 50 patients with chronic cough associated with bronchial asthma, pulmonary emphysema, and bronchiectasis, Tessalon afforded moderate to excellent relief in 70 per cent of the patients. Tessalon produced a mean increase of 20 per cent in the vital capacity in those patients with clinically demonstrable bronchospasm (Bickerman *et al.*, 1957).

When administered orally Tessalon evokes an effect within 10 to 20 minutes, and the duration is from 2 to 8 hours. There are no detectable cardiovascular effects from Tessalon and the incidence of side effects is low. Drowsiness, nausea, skin eruption, nasal congestion, dizziness, and a burning sensation in the eyes have been encountered. Habitutation, euphoria, respiratory depression, and constipation have not been reported following Tessalon. Although the controlled clinical trials with Tessalon are limited, it does appear that this drug represents an interesting and somewhat novel approach to cough suppression. The recommended dose is 100 mg. 3 to 6 times daily. The capsules are to be swallowed, not chewed.

**L-Propoxyphene (Novrad).** This agent is the levo isomer of dextropropoxyphene (page 461), a nonaddictive analgesic. Novrad elicits no analgesic action. Its principal response is antitussive. It compares favorably to 15 mg. of codeine in its antitussive activity, when employed in 50-mg. doses. The drug appears to be effective as an antitussive in about 80 per cent of the cases. Novrad is not constipative and tolerance does not develop with continued use. Nausea occurs in a small segment of patients; skin rash and drowsiness was observed also, but infrequently and generally when the usual dose of 50 to 100 mg. 3 times a day was exceeded.

**Dimethoxanate (Cothera).** Chemically, Cothera is an alkyl ester of phenothiazine. It evokes antitussive activity and is not addictive. A 25-mg. dose of Cothera is equipotent with 15 mg. of codeine. Side effects are reported as minimal. There have not been sufficient controlled clinical trials to establish the position of this agent as one of the effective nonaddictive antitussives.

It is encouraging to witness this frontal attack on cough with a variety of chemical structures of compounds that are nonaddictive. Despite these advances codeine remains still a formidable competitor. The annual production of this alkaloid continues to increase spectacularly, and its principal use is in the suppression of cough.

### Other Morphine and Codeine Derivatives

**Dihydrocodeinone Bitartrate, N.F.** Dihydrocodeinone bears the same relationship to codeine that dihydromorphinone (Dilaudid) bears to morphine. The secondary hydroxyl group is oxidized to a ketone, and the adjacent double bond is reduced by hydrogenation.

The action of dihydrocodeinone is similar to that of codeine. The compound is more potent and more prone to produce addiction than codeine. It is used mainly to suppress coughs. For this purpose there appears to be no distinct advantage over codeine. The dose of dihydrocodeinone is 5 to 15 mg. Dihydrocodeinone bitartrate is available in a tablet or syrup. The tablet contains 5 mg. of the codeine derivative and 1.5 mg. of homatropine methylbromide: it is called Hycodan.

**Ethylmorphine Hydrochloride, N.F. (Dionin).** The compound is soluble in 10 parts of water. As an analgesic it is comparable to codeine. Formerly it was widely used in the treatment of cough. It appears to offer no advantage over codeine in this respect. Its dosage schedule is the same as that for codeine.

Ethylmorphine hydrochloride is used in 2 to 5 per cent aqueous solution for instillation into the conjunctival sac. It produces hyperemia and a mild edema of the conjunctiva, referred to as *chemosis*. This irritative action lasts for 30 to 60 minutes. This is followed by a mild analgesia which is likely the result of the absorption of the drug. This action of the drug is employed to relieve deep-seated ocular pain as it occurs in iritis and to stimulate the healing of inflammatory processes.

**Dihydromorphinone Hydrochloride, U.S.P. (Dilaudid).** The compound is freely soluble in water. Dihydromorphinone is a more powerful analgesic than morphine. Its analgesic dose is approximately ⅕ that of morphine. With this dose dihydromorphinone produces less narcosis than morphine.

Dihydromorphinone is claimed to act more quickly than morphine. It is less constipative and less likely to produce anorexia, nausea, or vomiting. It does not constrict the pupil.

The drug produces euphoria and addiction, but the withdrawal symptoms which are produced by the removal of the drug are not so severe as with morphine.

The principal use of dihydromorphinone appears to be as a substitute for morphine, especially in intractable pain. For this purpose 3 mg. of dihydromorphinone confers the same degree of analgesia as does 15 mg. of morphine.

**Metopon** is methyldihydromorphinone hydrochloride. It is readily soluble in water. Although the experience with this drug is not so extensive as with the foregoing morphine derivatives, the following characteristics of the drug appear to be established. The drug is *twice as analgesic as morphine and devoid of emetic and respiratory responses in therapeutic doses.* In addition, Metopon exhibits its full analgesic effect when given orally. The effective oral analgesic dose is 5 mg. The side effects of an untoward character appear to be fewer after Metopon than after morphine. Metopon appears to be superior to morphine in the treatment of terminal carcinoma.

Metopon presents definite advantage for the ambulatory patient with intractable pain. It should be administered before tolerance to other opiates has been acquired. One may expect that Metopon will provide adequate analgesia for a longer period, often many weeks, without appreciable side reactions and drowsiness. The use of this drug in the United States appears to be very limited.

**Heroin** is diacetylmorphine. The hydrochloride is the most generally-used salt. It is freely soluble in water. Heroin is estimated to be 2.5 times more potent than morphine as an analgesic. Beecher *et al.* (1959) observed that heroin produced more mental clouding than did morphine. Of interest is the fact that 4 mg. of heroin was only slightly more depressant to the respiration than 10 mg. of morphine. Martin and Fraser (1961) found about the same ratio of potency between heroin and morphine when injected intravenously into postaddicts. Their studies indicated no clinical superiority of heroin over morphine. The dose of heroin is from 4 to 8 mg.

It was formerly considered that heroin evoked a more vicious type of addiction than morphine. The studies of Martin and Fraser indicate that postaddicts could identify the difference between the two drugs. Despite the ability to differentiate there appeared to be no overwhelming preference for heroin. The abstinence syndrome is of shorter duration with heroin than with morphine. The peak intensities were quite comparable. Because the drug offers no special advantage over morphine and other opiates, and owing to the widespread danger of heroin addiction, its manufacture in and importation to the United States are forbidden. Stocks on hand may be disposed of through regular medical channels.

The drug still appears on the illicit market. It has been unlawfully used to "dope" or stimulate race horses prior to races.

It is absorbed through unbroken mucous membranes and is frequently used as heroin snuff or "snow" by addicts. In recent years illicit heroin is often diluted 100 times by vendors before disposing of their product.

The blood slowly deacetylates heroin into morphine.

**Pantopon** is a mixture of the alkaloids of opium in the proportions in which they occur in the crude drug. They are sufficiently purified for injection purposes. Approximately ½ of the mixture is morphine.

*Pantopon appears to offer no special advantage over morphine in the relief of pain.* Wolff *et al.* (1940) did not find the analgesic action of Pantopon to be greater than that of morphine when it was evaluated on its morphine content.

The usual dose of Pantopon is 20 mg. It is given orally and parenterally. Pantopon is also called *Omnopon.*

**Apomorphine Hydrochloride, U.S.P.** is a product obtained from morphine by treatment with concentrated hydrochloric acid. Its structure is shown on page 356. It is soluble in 50 parts of water. The drug is subject to deterioration by exposure to light and air. Therefore the Pharmacopeia limits the size of the container to 350 mg. It must also be air-tight and light-resistant. Hypodermic tablets containing 5 mg. are also official.

Apomorphine is a centrally acting emetic. Its use today is almost entirely confined to this purpose. The drug is used to a limited extent in the treatment of bronchial asthma for the purpose of promoting the expulsion of mucus. Apomorphine exerts a direct stimulating action on the vomiting center and initiates emesis. It does not act locally as do mustard and tartar emetic.

When the vomiting center, located in the medulla, is stimulated reflexly or directly the following reflexes are initiated to produce vomiting. Nausea and salivation generally herald the emesis. The diaphragm descends. There is contraction of the respiratory muscles and the cardia is widely dilated. The pylorus is spastically contracted. The glottis closes as antiperistaltic waves ascend the esophagus. The posterior pillars of the fauces raise the palate to close the nasal cavity. The conditions are now set for the ejection of the gastric contents.

Hatcher and Weiss (1923) showed that apomorphine elicited the emetic response by its central action as follows:

1. Apomorphine is active when injected subcutaneously.
2. The vomiting reflexes were produced after extirpation of the gut and substitution by a balloon.
3. In the bilateral vagotomized animal locally acting emetics fail to produce emesis owing to the fact that the vagi serve as the afferent pathways for local emetics. In the vagotomized dog apomorphine is effective.
4. Upon the direct application of apomorphine to the *calamus scriptorius* emesis is evoked.

Borison and Wang (1953) and investigations by others have shed light upon the mechanism of emesis by various drugs. The mechanism of vomiting produced by apomorphine was studied by Borison and Wang in the dog. They observed that superficial medullary lesions with minimal damage to the *ala cinerea* abolished the emetic response to intravenous apomorphine and certain cardiac glycosides. In these animals, however, the oral emetic response to copper sulfate was not altered. When the lesions were deeper, involving the *lateral reticular formation*, the response to copper sulfate was also abolished. Borison and his associates interpret these responses to indicate that the vomiting center is located in the dorsal portion of the lateral reticular formation. Furthermore, there exists in the medullary surface a specialized *chemoreceptor trigger zone*. This in turn serves as the receptor site for centrally acting emetics. Thus drugs which produce vomiting by their central actions apparently may accomplish their effects through different mechanisms.

Man does not develop a tolerance to the emetic action of apomorphine as he does to the analgesic and euphoric action of morphine. Although apomorphine produces sedation there appears to be no marked tolerance to this response since it is blocked by the predominant emetic action.

The emetic dose of apomorphine is 5 mg. subcutaneously. When administered in poisoning to produce emesis the physician must be cautioned not to repeat the dose more than twice at half-hour intervals, owing to the toxic action of apomorphine.

**Apocodeine** bears the same chemical relation to codeine that apomorphine bears to morphine. It has no clinical application. It has been reported to produce a blockade of the autonomic nervous system.

**N-allylnormorphine** was studied by Hart and McCawley (1944). By replacing the N-methyl group in morphine by allyl, the respiratory depressant action disappeared. The analgesic activity was decreased. The constipative action of morphine on the gut was antgaonized by N-allylnormorphine. Indeed from the animal experiments, this compound appeared to warrant thorough clinical trial.

**Nalorphine Hydrochloride, U.S.P. (Nalline, N-Allylnormorphine Hydrochloride)** is available for use as an antagonist to the respiratory depressant action of morphine and other narcotic analgesics. The compound occurs as a white powder, readily soluble in water.

Eckenhoff *et al.* (1952) pointed out that nalorphine is valuable in respiratory depression caused by morphine, meperidine, and methadone. Further, it appeared useful in parturient women sedated with meperidine.

Nalorphine is administered intravenously in 5 to 10 mg. doses to increase pulmonary ventilation. If necessary, it may be repeated in 10 to 15 minutes. Within 2 minutes after the administration of the drug, a 200 to 300 per cent increase in respiratory minute volume may occur in depressed patients. Besides, the respiratory rate is increased 2- or 3-fold. Indeed nalorphine may completely abolish the respiratory depression of morphine if the former is administered prior to giving of morphine. Nalorphine will immediately precipitate the withdrawal syndrome in a morphine addict, page 391.

The drug appears well established as a respiratory stimulant and has already proved its value in various states of depressed respiration. Other groups on the nitrogen atom in morphine have not yielded useful competitors to the N-allyl substituted morphine or nalorphine.

Huggins and Moyer (1955) studied the action of nalorphine on normal individuals. They observed that it produced myosis, sweating, a slight degree of sedation, and hallucinations. The effects on respiration and the cardiovascular system were slight and variable.

Nalorphine does not produce serious toxic effects unless large doses are employed. The lethal dose has not been established for man; however, Wikler *et al.* (1953) showed that 75 mg. given to nontolerant former morphine addicts did not evoke dangerous symptoms. It is recommended that not more than 40 mg. be administered to adults in a single dose.

From available evidence it does appear that the antagonism to morphine intoxication elicited by nalorphine involves competitive inhibition at the receptor sites. A drug of weak narcotic activity (nalorphine) and of similar chemical constitution displaces one of pronounced narcotic activity (morphine) in the receptor sites of the target cells. The respiratory centers thus regain their normal sensitivity to carbon dioxide. Favoring the concept of competitive antagonism between the two compounds is the fact that nalorphine also antagonized the action of morphine on the gut. It is capable of blocking the antidiuretic action elicited by morphine in rats, page 362.

**Levallorphan Tartrate, U.S.P., Lorfan Tartrate.** *Levallorphan* is another antagonist to the toxic effects of morphine and other narcotic analgesics. This was shown in animals by Fromherz and Pellmont (1952). The compound is the N-allyl analog of Levo-Dromoran tartrate, page 378. Chemically levallorphan is *levo-3-hydroxy-N-allylmorphinan.* Several investigators have shown that in man the compound is an effective morphine antagonist. Mannering and Shanker (1958) studied the metabolic fate of levallorphan in several species of laboratory animals. All of the species studied showed the biotransformation of levallorphan into 3-hydroxymorphinan. Other metabolites were identified also.

Costa and Bonnycastle (1955) studied the comparative activity of nalorphine and levallorphan in rats. They found that each drug was effective in combatting the respiratory depression evoked by morphine, Levo-Dromoran, methadone, meperidine, and alphaprodine. They concluded that levallorphan was the more active antagonist.

Landmesser *et al.* (1955) studied levallorphan in man and compared its action with nalorphine. Each drug appeared equally effective in antagonizing the respiratory depression of the narcotic analgesics. It was ineffective against the respiratory depression produced by pentobarbital. These investigators used 0.5 mg. of levallorphan intravenously in their studies. It is clear that as an antagonist to morphine and related drugs, levallorphan is more potent than nalorphine. It remains to be established, however, that its use clinically can offer a substantial advantage over nalorphine. The following ratios of levallorphan are recommended to antagonize the narcotic-induced depression of the commonly used narcotic analgesics: morphine, 15 mg. to 0.3 mg. levallorphan; meperidine, 100 mg. to 1 mg. levallorphan; Levo-Dromoran, 3 mg. to 0.3 mg. levallorphan; and Nisentyl, 60 mg. to 1.2 mg. levallorphan.

Much interest has been aroused recently in the use of narcotic analgesics and their antagonists concomitantly in the relief of intractable pain, thus blocking the respiratory depressant action of the analgesic. Cullen and Santos (1954) used a combination of levorphan tartrate and levallorphan tartrate in an 8:1 or 10:1 ratio in the relief of chronic pain requiring narcotics. The narcotic antagonist caused no diminution in analgesia and blocked respiratory depression. The drugs were administered parenterally in a premixed solution.

Foldes and Lipschitz (1956) used a premixed solution of 40 mg. of Nisentyl and 0.8 mg. of levallorphan (50:1 ratio) to prevent respiratory depression of the mother and infant during labor. In 81.5 per cent of their cases they considered the effects of the mixture excellent.

Numerous other investigations have been conducted studying the combined effect of narcotic and narcotic-antagonist mixtures. The subject was reviewed critically by Telford and Keats (1961). They concluded from the data available in animals and man, as well as from theoretical considerations, that the objective of lesser respiratory depression is not likely to be achieved with the drugs now available.

**Papaverine.** This alkaloid of opium is discussed under the section on the circulation, page 671, owing to the fact that this alkaloid of opium is used primarily in the treatment of coronary insufficiency.

Macris and associates (1958) observed a synergistic action elicited by papaverine with the analgesic action of morphine. Their study was carried out on patients with postoperative pain. They observed that when 10 mg. of morphine was preceded by the administration of 50 mg. of papaverine, the analgesic effect of morphine was significantly enhanced. Since papaverine is not an analgesic it appears that its presence in the tissues synergizes the analgesia evoked by morphine.

### NEWER MORPHINE DERIVATIVES

The search for newer morphine derivatives with more potency, less untoward side effects and less addictive hazard continues with avidity. Newer methods of organic synthesis and more critical methods of pharmacologic and clinical evaluation have lent impetus to this search.

*Normorphine* has been studied by various investigators who observed it to be less potent as an analgesic than morphine (Eddy *et al.*, 1956). Lasagna and DeKornfeld (1958) studied normorphine on patients suffering with postoperative pain. They observed that its potency as an analgesic was ¼ that of morphine. They suggest that it is unlikely that morphine must undergo N-demethylation before evoking its analgesic effect in man.

*Oxymorphone, Numorphan.* Oxymorphone is 14-hydroxydihydromorphinone. Coblentz and Bierman (1956) observed that oxymorphone was approximately 8 times more potent than morphine in patients with chronic pain. Eddy and Lee (1959) studied the two drugs in patients with chronic pain owing to neoplastic disease and controlled their studies with placebos. They found an approximate ratio of 10 to 1 in analgesic potency in favor of oxymorphone. The two drugs were not significantly different in peak or duration of effect. Oxymorphone appeared to evoke less nausea and vomiting. They assert, "An increase in the dose of oxymorphone, however, increases the side effects and may be accompanied by severe respiratory depression in debilitated individuals, possibly to a greater extent than with morphine."

**Phenazocine Hydrobromide, Prinadol Hydrobromide.** Phenazocine is a potent narcotic analgesic; a derivative of *benzomorphan.* Chemically the compound is 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-phenethyl-2,6-methano-3-benzazocine hydrobromide. The analgesia evoked is similar to that of morphine; however, the effective dose of phenazocine is much smaller. The sedation elicited by phenazocine appears to be less than that produced by morphine, but respiratory depression occurs after its use. The addictive hazard of phenazocine is comparable to that of morphine.

Berkowitz *et al.* (1961) studied the relative respiratory depression of phenazocine and morphine in normal persons and patients. They found that 4 mg. of phenazocine depressed the respiration more profoundly than did 15 mg. of morphine. Other side effects of phenazocine encountered are nausea, vomiting and hypotension. Like morphine, the analgesic is constipative. The recommended dose of phenazocine is 2 mg. every 4 to 6 hours intramuscularly as needed.

**Benzomorphan Analgesics.** Several benzomorphan derivatives are under investigation as morphine substitutes. Archer *et al.* (1962) observed that 2-dimethylallyl-5,9-dimethyl-2′-hydroxybenzomorphan, Pentazocine was a weak antagonist of morphine and meperidine. In patients, 20 mg. of the benzomorphan derivative showed an analgesic potency equal to 10 mg. of morphine. The psychic effects evoked by nalorphine were not experienced. Sedation and vertigo occurred with increasing dosage. Of special interest is the finding of Seevers and Deneau (1962) that physical dependence could not be established with the drug in monkeys. The addiction liability in man is being assessed at present. Should the compound prove to be nonaddictive, it will likely bid fair to be a major step in dissociating potent analgesia evoked by a drug from addictive hazard.

It appears that certain of the addictive narcotic antagonists, which are derivatives of *benzomorphan*, exhibit profound analgesia without physical dependence. The acquiring of tolerance by the patient to the analgesic action has not been adequately explored.

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# 24

# *Central Nervous System Depressants. Other Addictive Analgesics, and Marihuana*

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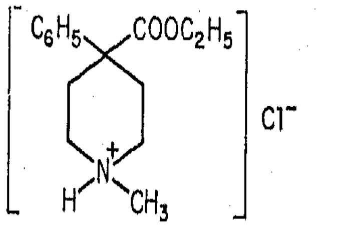
The effort to synthesize a drug that produces the analgesia of morphine has been unrelenting. Besides, the pharmacologist has sought compounds which, although analgesic, would be devoid of the vicious addictive action of morphine and many of its derivatives. For many years this search was fruitless. The effort, however, was untiring and recently much progress has been made. The progress in the field has resulted from the ever-increasing skill of the organic chemist in synthesis and the recent development of pharmacologic methods to measure quantitatively pain intensity and its relief by drugs. The first drug of analgesic power comparable to the opiates to warrant clinical use was *Meperidine Hydrochloride.*

**Meperidine Hydrochloride, U.S.P.** This drug is also known as *Demerol, Isonipecaine Hydrochloride* and *Pethidine.* Meperidine was synthesized by Eisleb and Schaumann in 1939 in an effort to obtain a drug similar to atropine, possessing spasmolytic activity. This was achieved. It was discovered also that the compound evoked analgesia and produced sedation. The structure of meperidine is shown in the following formula:



Meperidine Hydrochloride, U.S.P.
Demerol
(ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride)

It is a white, crystalline powder, slightly soluble in water. The free base exhibits a strong alkaline reaction; the hydrochloride is neutral.

**Analgesia with meperidine.** The analgesic properties of meperidine were investigated in man by Tainter (1948). He measured the increase in pain threshold upon intramuscular injection of meperidine and codeine, using a modified Wolff-Hardy technic. His results are shown in figure 24-1.

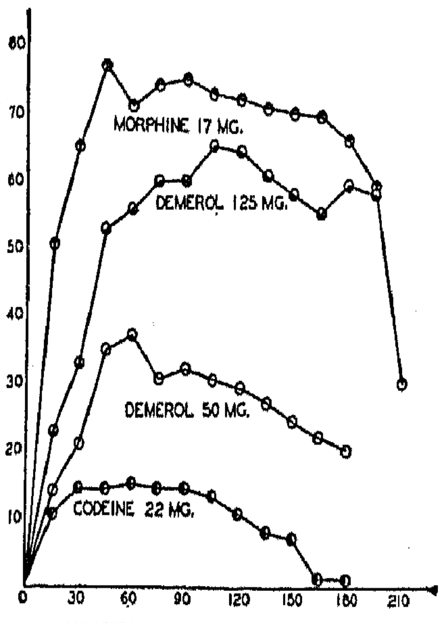


FIG. 24-1. Comparison of analgesic power of morphine, demerol (meperidine) and codeine in human subjects when tested by the pain threshold of the skin to heat stimuli. The curves are the averages of 16 experiments. (*Tainter, 1948.*)

An examination of the chart shows meperidine to be superior to codeine as an analgesic. This investigator compared the drug to morphine by the same technic and found meperidine analgesia to be inferior to that of morphine. *The analgesic effect of meperidine appears to lie intermediate between codeine and morphine.* It is not valuable in the treatment of cough.

**Spasmolytic action of meperidine.** This drug has been tested by the classical methods of evaluating spasmolytics. In the usual test preparations meperidine in high dilutions was found to relax the intestine, the bronchi, ureter, and uterus. As a relaxant to smooth muscle 20 mg. of meperidine is equivalent to 0.6 mg. of atropine.

Pickering *et al.* (1949) reinvestigated the spasmolytic action of meperidine. They showed that the atropine-like action of the drug could not be demonstrated on the small intestine, extra-hepatic biliary tract, or the cardiovascular system in the dog. They prefer to classify meperidine with an action similar to morphine on the structures innervated by the autonomic nervous system rather than atropine-like in character.

It was shown by Gruber, Jr., *et al.* (1950) that meperidine evoked a loss of general tonus and a decrease in the height of the rhythmic contractions of the excised rabbit's intestines. The action is similar to that evoked by methadone but more powerful.

**Sedative action of meperidine.** Meperidine is not a powerful hypnotic. It does, however, potentiate the action of other sedatives (Rovenstine and Batterman, 1943). It has been used quite successfully as premedication in anesthesia. Approximately ½ of the individuals taking the drug (100 mg.) experience sedation to the point of hypnosis. In others it serves only as a mild sedative or produces no central nervous system depression.

**Meperidine on the circulation.** Gruber *et al.* (1941) administered meperidine to dogs intravenously 0.25 mg./kg. There was observed a fall in blood pressure which was attributed to peripheral vasodilation. Depression of the cardiac vagus was observed. The drug probably acts at the postganglionic vagal nerve endings.

**Fate of meperidine.** The drug is destroyed in the liver for the most part. A small portion is excreted in the urine. Way *et al.* (1947) produced additional evidence to show that the liver is the site of the inactivation of meperidine. Meperidine is metabolized in man at the rate of 17 per cent per hour. Its biologic half-life period is 3 to 4 hours with a considerable degree of variability in different individuals. The relatively short half-life period of meperidine in the body provides an explanation for the necessity of frequently repeating the dose for the continuous relief of pain. In the metabolic process a portion of the meperidine is demethylated, another fraction is de-esterified, and about 5 per cent of the dose is excreted unchanged (Burns *et al.*, 1955).

**Untoward effects of meperidine.** Dizziness is the most frequently encountered untoward effect produced by meperidine. It may be noted in 60 per cent of the patients receiving the drug. Operating a motor vehicle after the taking of meperidine may be hazardous. Nausea and vomiting are less frequently observed. Profuse sweating is a frequent finding. Batterman (1944) observed 4000 cases to whom meperidine had been administered. He stated that the drug was rela-

TABLE 24-1

*Meperidine in Pain*

(Yonkman *et al.*, 1944)

| Type of Pain | No. of Cases | Complete Relief | Partial Relief | No Relief |
|---|---|---|---|---|
| Arthritic | 9 | 6 | 2 | 1 |
| Gastrointestinal | 22 | 15 | 6 | 1 |
| Biliary tract | 5 | 3 | 1 | 1 |
| Renal | 6 | 6 | | |
| Neural and thalamic | 18 | 11 | 6 | 1 |
| Osseous | 8 | 3 | 2 | 3 |
| Headache | 18 | 13 | 2 | 3 |
| Pleural | 12 | 8 | 2 | 2 |
| Cardiac | 10 | 5 | 4 | 1 |
| Miscellaneous | 15 | 9 | 4 | 2 |
| Total | 123 | 79 (64.2%) | 29 (23.6%) | 15 (12.2%) |

tively safe, and the chief untoward effect was that of "cerebral irritability" with large doses.

Euphoria is sometimes noted. The drug is potentially habit-forming. Tolerance appears to develop with its use.

Prolonged administration of meperidine elicits only mild depression of the respiration and circulation. Kidney function and the hematopoietic system are not impaired. Sweating and xerostomia may be marked. Large doses of meperidine may evoke tremors and even convulsions. Respiratory depression induced by an overdose of meperidine may be effectively antagonized by the intravenous administration of 10 to 40 mg. of nalorphine (Eckenhoff *et al.*, 1952).

**Addiction.** Meperidine produces habituation and dependence. This is not so readily developed nor is it so vicious as with morphine. Andrews (1942) studied the electroencephalograms of individuals receiving meperidine for 50 to 70 days. He reported a distortion of the normal pattern—"slow waves were seen early in the study under meperidine, and these became progressively slower and of greater amplitude, persisting for 48 hours after the withdrawal of the drug and slowly returning to normal."

The incidence of addiction to meperidine is high among physicians and nurses, partly owing to the fact that many do not recognize its addictive hazard. Between July 1, 1950, and July 1, 1951, 268 primary meperidine addicts were admitted to the Lexington Public Health Service Hospital. Forty-four of the addicts were physicians and 44 were nurses. In the group also were 9 medical technicians or nurses aides (Isbell and White, 1953).

Chronic intoxication with meperidine occurs when daily dosage levels of 2000 to 3000 mg. are administered. Myoclonic jerks and generalized convulsive seizures may occur. Acute withdrawal of meperidine, in addition to producing extreme restlessness, anxiety and sweating, evokes muscle jerks similar to the toxic syndrome. This similarity between the toxic and the withdrawal syndrome renders the two difficult to distinguish. It has recommended in such cases to reduce the daily dose of meperidine, while increasing the frequency of administration, until a subconvulsive level is achieved. At this time the meperidine dosage is gradually withdrawn substituting methadone as is recommended under morphine addiction.

Meperidine was classified as a narcotic under the Harrison Act, July 1, 1944.

### The therapeutic uses of meperidine.

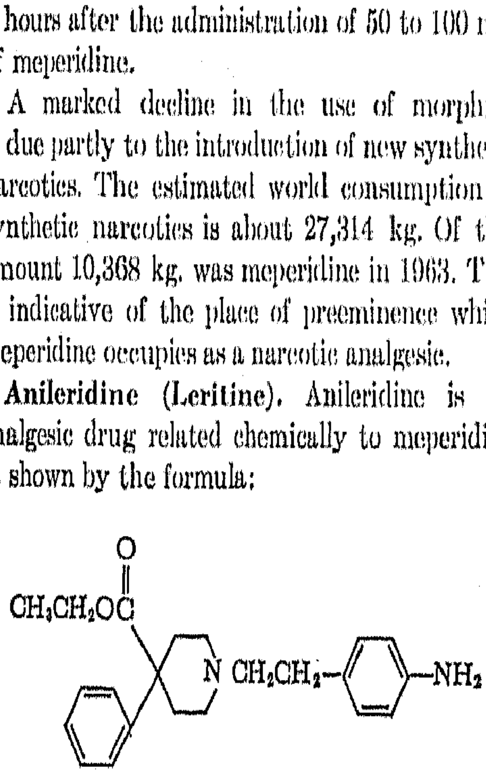
1. The principal use of meperidine is to relieve pain. Yonkman *et al.* (1944) used meperidine in 123 patients with diseases producing pain sufficient to justify opiates. Their results are shown in table 24-1.

   Dripps *et al.* (1957) found equipotent dosage ratios upon intramuscular injection of morphine and meperidine to be 1 to 3.5 to 5. The duration of analgesia was 58 minutes for meperidine and 72 minutes for morphine.
2. Meperidine is valuable in premedication for anesthesia.
3. Meperidine is used in the treatment of bronchial asthma. It is employed in the acute attack or in status asthmaticus when epinephrine and aminophylline have failed. Herschfus *et al.* (1954) demonstrated that 100 mg. of meperidine given subcutaneously to the asthmatic patient provided adequate anticholinergic action and moderate antihistaminic effects. Side reactions were found to be few. The danger of addiction enjoins one, however, to use meperidine in asthma only when other standard procedures of treatment have failed.
4. Meperidine is used to produce analgesia during labor. For this purpose it may be combined with scopolamine or the barbiturates. Gordon and Pinker (1958) found an injection of 10 mg. of nalorphine useful in obstetrical patients given meperidine in large doses. The nalorphine was administered 5 minutes before delivery was expected.

**Dosage of meperidine.** Meperidine is usually administered orally or intramuscularly. It may be given intravenously. The dose ranges from 25 to 150 mg. Oral administration is preferable when long-continued use is necessary for the relief of chronic pain. The compound should be administered intramuscularly for the rapid relief of severe pain. The analgesia continues for approximately 3 hours after the administration of 50 to 100 mg. of meperidine.

A marked decline in the use of morphine is due partly to the introduction of new synthetic narcotics. The estimated world consumption of synthetic narcotics is about 27,314 kg. Of this amount 10,368 kg. was meperidine in 1963. This is indicative of the place of preeminence which meperidine occupies as a narcotic analgesic.

**Anileridine (Leritine).** Anileridine is an analgesic drug related chemically to meperidine as shown by the formula:



Anileridine (Leritine)

(ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate)

Anileridine is available as a dihydrochloride for oral use and a phosphate for parenteral administration. Each is a white crystalline powder, soluble in water.

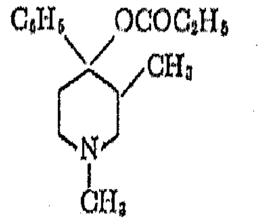
The analgesic activity of anileridine is 3 to 6 times greater than that of meperidine but somewhat less than that of morphine. Unlike meperidine, anileridine elicits an antitussive action. Its side reactions are few; nausea, vomiting, and constipation have not been encountered with its use. The acute toxicity of anileridine in animals is of the same order of magnitude as that of meperidine. The action of anileridine is antagonized by nalorphine. The liability of addiction to anileridine is equivalent to that of morphine.

Studies in man indicate that anileridine is a potent analgesic agent. In patients suffering with pain owing to malignancy or surgery, oral or subcutaneous doses of the drug, 15 to 30 mg., has afforded relief. As in laboratory animals these observations in man pointed to an analgesic potency of ⅓ to ⅕ that of morphine and 2 to 3 times that of meperidine.

Dripps *et al.* (1957) studied the effect of anileridine, morphine, and meperidine in achieving analgesia from postoperative pain. The equipotent analgesic doses upon intramuscular injection were found to be: morphine, 1; anileridine, 2 to 2.5; and meperidine, 3.5 to 5. The duration of action of anileridine was 50 minutes, meperidine, 58 minutes, and morphine, 72 minutes. Keats *et al.* (1957) found 40 mg. of anileridine to be as potent as 100 mg. of meperidine. They also observed that anileridine depressed the respiration to the same degree as did meperidine, however the depression was of shorter duration.

Chang *et al.* (1958) evaluated the comparative potency of anileridine and meperidine by studying their capacity to reinforce the action of nitrous oxide under controlled conditions. They concluded that anileridine is a potent narcotic which is not superior to meperidine. Their data suggest that anileridine is more depressant to the respiration than meperidine when administered in equipotent analgesic doses.

**Nisentil Hydrochloride (Alphaprodine Hydrochloride).** One of the analgesic drugs of the piperidine series is alphaprodine, available as the hydrochloride. The compound is the hydrochloride of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine, as shown in the accompanying formula.



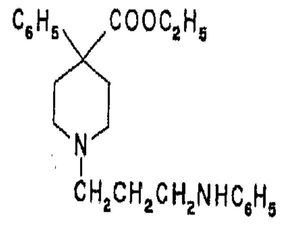
Alphaprodine (Nisentil)

The compound is recommended for obstetrical analgesia. It is given by subcutaneous injection of 40 mg. (1 ml.) at least at 2-hour intervals. The last dose should be given 2 hours or more prior to delivery. Hapke and Barnes (1949) found alphaprodine a useful adjunct in producing obstetrical analgesia. In a carefully controlled series of cases they observed little evidence of fetal respiratory depression. Smith and Nagyfy

(1949) found alphaprodine to compare favorably with other drugs used as analgesics in obstetrics. They were especially impressed by its short duration of action, which provided greater flexibility. Nausea and emesis were encountered as side effects in some patients. Kane (1953) used alphaprodine in 1000 deliveries and recorded satisfactory obtunding of pain in 981 cases. Its advantage over meperidine is its greater potency with a similar margin of safety.

Alphaprodine evokes a minimum of cumulative action. Tolerance can develop with repeated use and the drug possesses a definite liability of addiction.

**Alvodine (Piminodine).** Alvodine is an addictive analgesic of the piperidine series that is as potent as morphine. It is available as its ethanesulfonate. The structure is shown in the formula.



Alvodine, Piminodine
ethyl 4-phenyl-1-[3-(phenylamino)-propyl]-piperidine-4-carboxylate

The ethanesulfonate of Alvodine occurs as a white, crystalline solid that evokes a bitter taste.

**Pharmacologic studies.** In mice, rats, and monkeys employing the experimental procedures of measuring analgesic potency, Alvodine was found to be more potent than morphine. Its latent period of activity was similar to that of morphine and the duration of analgesia approximately the same. The acute toxicity of Alvodine upon subcutaneous injection in rats was less than that of morphine. The therapeutic index ($LD_{50}/ED_{50}$) in rats was found to be 24.5 for morphine and 50.0 for Alvodine.

The depressor response in dogs upon intravenous injection was less than that elicited by morphine. Like morphine, Alvodine was found to depress respiration.

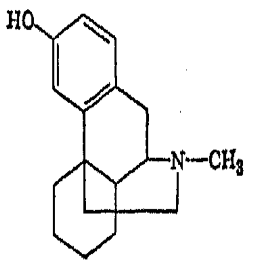
**Clinical use of Alvodine.** Alvodine is used in severe pain similar to the other addictive analgesics. In a double blind study DeKornfeld and Lasagna (1959) found 7.5 mg. of Alvodine equivalent to 10 mg. of morphine in the relief of postoperative pain. Side effects appeared to be minimal even when the dose was increased to 20 mg. Dornette *et al.* (1961) used Alvodine 10 to 20 mg. intramuscularly or subcutaneously prior to anesthesia. They observed a relief from anxiety and smooth induction of anesthesia followed.

Side effects encountered with Alvodine have been few and not severe. The analgesic dose produces a minimum of drowsiness and euphoria. Unsteadiness of gait has been observed in a segment of the patients. The absence of constipative action upon prolonged use is a definite asset of the drug.

The indication is that the addictive hazard of Alvodine is comparable to that of morphine. Its respiratory depressant action is antagonized by nalorphine.

Alvodine is given subcutaneously or intramuscularly in 10 to 20 mg. doses every 4 hours when needed. It is also effective orally in 25, 50, and in severe pain 100 mg. every 4 to 6 hours as required.

**Levo-Dromoran Tartrate (Levorphanol Tartrate).** Levo-Dromoran tartrate is the tartaric acid salt of 3-hydroxy-N-methylmorphinan as shown in the formula.



Levo-Dromoran
Levorphanol

Levo-Dromoran tartrate occurs as a white crystalline powder. It is soluble in water to the extent of 2 per cent.

Dromoran is the *d,l* form of the morphine derivative. It has been shown that the effectiveness of the compound as an analgesic resides in the *levo* form. Hunt and Foldes (1953) found 3-mg. doses of the *levo* isomer to be the analgesic equivalent of 5 mg. of *d,l*-Dromoran. The dextro isomer is not analgesic in its action but antitussive similar to codeine. It is available under the name of Romilar, page 365.

This synthetic analgesic is a potent addictive drug with properties similar to morphine, methadone, and meperidine. When administered subcutaneously, Levo-Dromoran is more potent and longer acting than morphine. Its margin of safety is approximately equal to that of morphine. Levo-Dromoran depresses respiration to approximately the same degree as morphine but less than methadone. Levo-Dromoran is used for relief of severe pain. It is generally administered subcutaneously in doses from 2.5 to 5 mg. Levo-Dromoran presents a definite addiction hazard.

From data of various investigators it is clear that 2 to 3 mg. of Levo-Dromoran provide the same degree of analgesia as 10 to 15 mg. of morphine. The side effects are similar to those of morphine, except that constipation is not produced.

Gaard (1955) used Levo-Dromoran in 100 postoperative cases for the relief of pain. He was favorably impressed by the analgesia and the absence of side effects. Its effectiveness in children was stressed. Emmons *et al.* (1955) in a similar series of cases were favorably impressed by the analgesia induced by Levo-Dromoran. Parenterally 2 mg. of the drug were effective in 96 per cent of the cases. Orally 1.5 mg. provided adequate relief in 55 per cent of the trials.

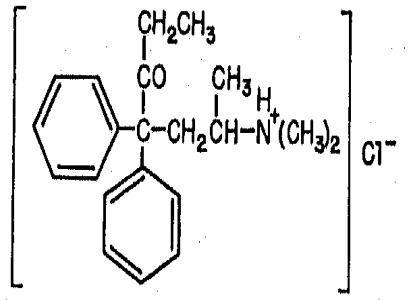
Overdosage with Levo-Dromoran is effectively combated by the administration of nalorphine or levallorphan. This compound appears to be a useful addition to the group of analgesic narcotics.

### METHADONE HYDROCHLORIDE, U.S.P.

**Methadone Hydrochloride, U.S.P.** is a synthetic analgesic drug. It is known as *Amidone*, *Dolophine*, or *Adanon*. It was obtained by American scientists from Germany after World War II. It was synthesized first in 1941, but its pharmacologic properties were not thoroughly investigated. The structure of methadone is shown in the accompanying formula.

It is a white, crystalline substance which is readily soluble in water. It elicits a bitter taste.

**Analgesia with methadone.** In various laboratory animals methadone has been shown to raise the threshold to pain. Methadone, 2.5 to 5 mg., raised the pain threshold more than did 10 mg. of morphine.



Methadone Hydrochloride, U.S.P.
(6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride)

**Methadone on the central nervous system and circulation.** When administered to unanesthetized dogs, methadone produces a slowing of respiration, vagal stimulation, with concomitant bradycardia, and some salivation. In rats, mice, and cats it produces a typical morphine response.

In man, to whom 15 mg. of methadone was administered subcutaneously, the minute volume of expired air was reduced about 14 per cent. In other individuals who received from 4 to 6 doses of 7.5 mg. at 4-hour intervals, the reduction was about 20 per cent in minute volume. Like morphine, methadone depresses the cough center. In the 2 series of cases there were no detectable changes in blood pressure, pulse, or electrocardiogram.

The comparison of the effects of morphine and methadone on the blood pressure and respiration of anesthetized dogs is shown in figure 24-2 (Chen, 1948).

The effect of methadone on the metabolism of brain tissue has been studied by various investigators. Elliott *et al.* (1947), using pieces of human cortex, observed an inhibition of glucose utilization with 0.002 M methadone solution. Miller and Elliott (1954) using rat's brain slices showed that methadone elicited a diphasic action on the oxygen uptake of the tissue. In low concentrations the oxygen consumption was increased; at higher levels it was depressed. The initial stimulating action was found to be reversible by the washing of the tissue; the inhibitory action of higher concentrations was not reversed by this procedure. Watts (1950) studied methadone and its isomers on the metabolism of rats' brain homogenates. The oxidation of glucose was inhibited to varying degrees by methadone and its isomers. The anaerobic glycolysis of glucose, however, was markedly accelerated. Succinate oxidation was inhibited. It is clear that methadone exerts a profound effect upon the metabolism of brain tissue.

**Methadone on the intestine.** Scott and Chen (1946) observed that methadone increased the tone and amplitude of contractions in the intestine in trained, unanesthetized dogs. This action resembles the response evoked by morphine.

**Fate of methadone.** The fate of methadone in the body has not been completely determined. From ⅙ to ⅓ of the drug administered is excreted in the urine by man (Scott and Chen, 1946).

Way *et al.* (1951) demonstrated that methadone

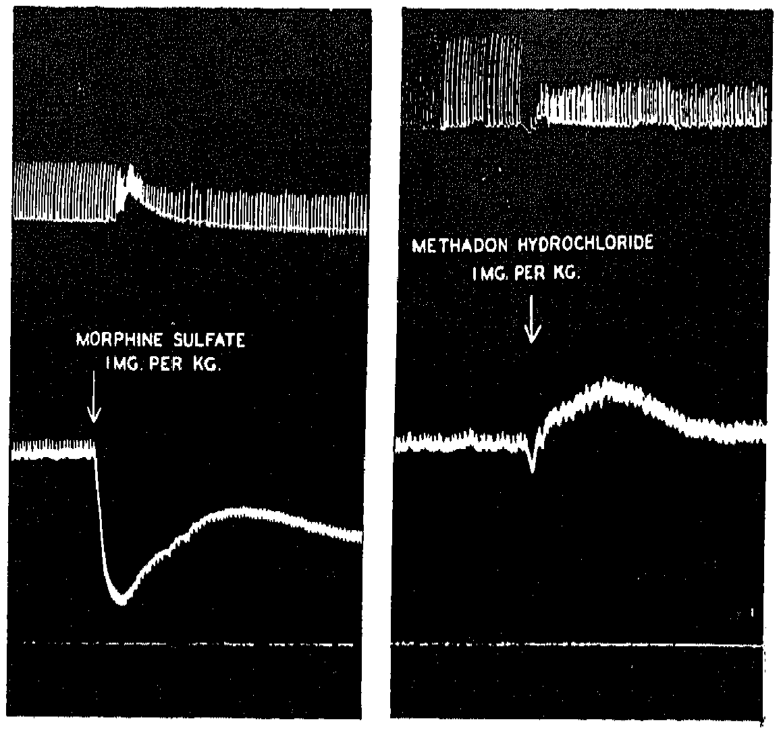


Fig. 24-2. Action of methadone and morphine on the blood pressure and respiration of anesthetized dogs. (*Chen, 1948.*) The injections were made intravenously.

was well absorbed from the gastrointestinal tract. The compound is concentrated in the liver, kidneys, lungs, and spleen. Blood levels are low, and these lower concentrations are shared by the heart and muscle. Only a very small fraction of the compound appears in the urine and feces unchanged.

Sung and Way (1950) found the toxicity of methadone greatly increased in laboratory animals after partial hepatectomy. The liver was found to be the principal site of metabolism for *d,l*-methadone. In incubation studies with tissue slices the liver rapidly metabolized the compound at pH 7.5 to 8.5. The metabolic process was sharply diminished by a pH shift to either the acid or alkaline side of the optimal value. When the liver is partially removed, tissue concentrations of *d,l*-methadone in the heart, lungs, spleen, and kidneys are concomitantly increased. Sung and Way (1953) made the interesting observation, that although the *d*- and *l*-isomers differ greatly in their pharmacologic response, only minor differences were observed in the distribution and excretion of each isomer. The rate of metabolism by liver slices is about the same for each isomer and each was affected to the same degree by enzyme inhibitors. The metabolic pathways of the 2 isomers appear to be essentially the same.

**Tolerance with methadone.** Repetitious doses of morphine to dogs produce definite tolerance when measured by the increased threshold to pain. This does not obtain to the same degree with methadone.

During experimental addiction to methadone in human subjects definite tolerance was found to develop. Isbell *et al.* (1948) observed that tolerance was developed to the *sedative*, *emetic*, *myotic*, and *analgesic* responses to the drug.

**Untoward effects of methadone.** Many untoward side effects have been recorded after the administration of methadone. Among these are nausea, vomiting, light-headedness, drowsiness, xerostomia, diaphoresis, and mental depression. These effects occur more frequently in ambulatory patients than in bed patients. Like morphine, methadone produces myosis.

**The addictive properties of methadone.** The addictive properties of methadone have been extensively investigated. Isbell *et al.* (1947) observed that the drug provided complete satisfaction to morphine addicts. In blind experiments, addicts could not distinguish between injections of morphine, heroin, dihydromorphinone, or methadone. Some individuals who were experimentally addicted to methadone seemed to prefer morphine to that drug. On the other hand, individuals who were given methadone injections appeared to enjoy an intensive false euphoria (Isbell, 1948).

The behavior pattern of individuals addicted to methadone is similar to that of the morphine addict. Productive activity ceases. They become untidy about themselves and their quarters. They prefer to remain in bed in a state of somnolent passivity which they regard as pleasurable. Pleas for increasing dosage levels are frequent during addiction.

TABLE 24-2

*Comparative Efficacy of Single Doses of New Drugs in Altering Various Factors Concerned in Analgesia**

(Vogel et al., 1948)

| Drug | Dose | Elevation of Pain Threshold | Alteration of Reaction of Pain | Sedation | Duration of Clinical Relief of Pain |
|---|---|---|---|---|---|
| | *mg.* | | | | *hr.* |
| Morphine | 10 | 2 | 2 | 1 | 4 |
| Metopon | 6 | 1 | 1 | 3 | 4 |
| Meperidine hydrochloride | 100 | 4 | 3 | 2 | 3 |
| Methadone | 5–10 | 3 | 4 | 4 | 4–10 |
| Codeine | 30 | 5 | 5 | 5 | 4 |

* The figure 1 indicates the most effective of the drugs.

Methadone served to relieve completely the abstinence syndrome of morphine addiction. When methadone was abruptly withdrawn from an addict, no complaints were forthcoming until the third or fourth day. He then complained of *fatigue*, *weakness*, *anxiety*, *vague abdominal discomfort*, and *hot* and *cold flashes*. The objective symptoms of autonomic imbalance were much less marked than after morphine withdrawal. Body temperature, pulse and respiratory rates, and systolic blood pressure were increased. It appears that abstinence symptoms from the withdrawal of methadone are slower to make their appearance than with morphine. The course of symptoms with methadone withdrawal are more prolonged but not so severe as after morphine withdrawal.

**Methadone, morphine, and meperidine.** Troxil (1948) compared the action of morphine, methadone, and meperidine clinically. She made the following observations:

1. Methadone has characteristics of both morphine and meperidine.
2. Oral use of the elixir is almost as effective as the hypodermic injection.
3. Ten mg. of methadone is as effective in relieving pain as 15 mg. of morphine or 150 mg. of meperidine.
4. Adequate or complete relief of pain occurred in 81 per cent of 400 patients.
5. Less sedation and euphoria occur with methadone than with morphine.
6. Side effects occurred in 13 per cent of patients.
7. Tolerance to the drug may develop.

In table 24-2 the comparative analgesic action of the principal narcotic type analgesics is given.

**The therapeutic uses and dosage of methadone.**

1. The principal use of methadone is to relieve pain in cases where nonaddictive analgesics have failed or are considered to be ineffective.
2. Methadone appears to be useful in renal colic.
3. Methadone has been used successfully in the treatment of severe cough (pulmonary tuberculosis and bronchiectasis).

Methadone is given in 5-mg. doses orally for moderate pain. It is repeated every 3 or 4 hours. For severe pain 15 mg. may be required. For acute, excruciating pain, 10 mg. subcutaneously are recommended.

Methadone is classified as a narcotic under the Harrison Narcotic Act (1947). Approximately 252 kg. of methadone were used in the United States in 1954. By 1963 this quantity dropped to 85 kg. It appears that the use of methadone is significantly diminishing.

**Isomers and analogs of methadone.** Methadone as generally employed is the *d,l*-form of the molecule. The dextro and levo isomers have been resolved and have been the subject of much experimental and clinical investigation. Chen (1948) found *l*-methadone to be 7 times more potent as an analgesic in rats than *d*-methadone. Despite the greater analgesic potency of the levo isomer, it is not localized in the brain to any greater extent than is the dextro compound (Sung and Way, 1953). In larger animals the difference in analgesic potency appears to be enhanced. Indeed in man the levo variety has been observed to be about 50 times more potent than the dextro compound. It is of interest that the intravenous fatal dose of the 2 isomers in mice is about the same. The racemic mixture appears to be definitely more toxic in mice than either isomer.

Chen and associates (1948) have synthesized more than 200 compounds related to methadone. The elimination of the amino-N atom destroys completely the activity of the compound. The ketonic and amino groups must be on opposite sides of the diphenyl C-atom. If they occur on the same side, activity is lost. Substitution of other rings for the phenyl groups, such as benzyl and cyclohexyl, has been disappointing. The most promising member of this large series of compounds was only 1/33 as active as methadone.

**Dextromoramide (Dimorlin, Palfium).** The analgesia of Dextromoramide in mice was described by Janssen and Jageneau (1957). Chemically Dextromoramide is *d*-1-(3-methyl-4-morpholeno-2,2-diphenyl-butyryl) pyrrolidine. The analgesic potency of Dextromoramide was confirmed in man by Boudin and Barbizet (1958). Cahal (1958) observed an elevation of the pain threshold in experimental pain in volunteers with parenteral doses of 3 to 10 mg. of Dextromoramide. There was, however, a high incidence of unpleasant side effects.

Lasagna *et al.* (1958) studied Dextromoramide in controlled clinical pain by oral and parenteral administration. Dextromoramide compared favorably with morphine and meperidine in the relief of postpartum pain. Dizziness and nausea were frequent side effects when Dextromoramide was given orally. Vomiting was encountered as a side effect of Dextromoramide only when it was administered parenterally. These investigators are of the opinion that Dextromoramide and methadone are about equipotent when administered parenterally. In this series of cases approximately ½ of the patients experienced side effects compared to 25 per cent with meperidine and 11 per cent with morphine.

It does not appear that Dextromoramide offers any advantage over methadone, which it resembles in chemical constitution.

## Marihuana (Cannabis)

Cannabis is "the dried flowering tops of the pistillate plants of *Cannabis sativa* (*Fam. Moraceae*) grown in the East Indies and gathered while the fruits are yet undeveloped and are carrying the whole of the natural resin." The plant is grown extensively throughout the world for hemp fiber and seed. Much of it grows in America.

**Constituents of cannabis.** Cannabis, as collected, contains from 5 to 8 per cent of resin. An alcohol obtained from the resin is active upon the central nervous system. A volatile oil is also present in the plant and 2 or more alkaloids which are not active pharmacologically.

**Cannabinol.** Cannabinol, one of the alcohols present in cannabis, is very toxic but does not elicit typical marihuana activity. Adams *et al.* (1940) obtained *cannabidiol* from the red oil of Minnesota wild hemp. They found that many of its derivatives were active in evoking the typical narcotic effect of marihuana. A very active cannabidiol derivative is *tetrahydrocannabidiol.*

Adams *et al.* (1942) synthesized a number of the tetrahydrocannabinol homologs and analogs. These were found to elicit marihuana activity.

**Action of cannabis on the central nervous system.** Cannabis was known to the Chinese 500 years before the birth of Christ. In the eleventh century Hassan ben Sabah, a friend of Omar Khayyam, organized a group of assassins who were given cannabis or "hashish" before committing their bloody crimes. Cannabis offered an escape from reality. Illegitimately, cannabis is used in this country for this purpose. It has been termed the "Assassin of Youth."

The effect on the brain of ingesting or smoking marihuana is different for various individuals. It perverts perception. Time, distance, and sound are magnified. Delightful intoxicating dreams of voluptuous nature are said to be experienced by some individuals. Large habitual doses may bloat the face, make the legs tremulous and weak, and may cause mental and moral degeneration.

LaGuardia's Committee on marihuana investigated the use of the drug in New York City (1944). The Committee reported more than 500 vendors of the drug in New York City. The use was confined almost exclusively to the smoking of cigarettes. The cigarettes were smoked most frequently in company with others in especially decorated incense-laden rooms called "tea-pads." Several hundred of these "tea-pads" were found in Harlem. The highest percentage of marihuana smokers was found among Negroes.

The Committee's investigation showed that marihuana smoking did not produce a tolerance for the drug or a true addiction with withdrawal

symptoms. The sensations desired by the habitués were a feeling of contentment, inner satisfaction, and a free play of the imagination. The relation between marihuana usage and eroticism was found capricious. One of the greatest dangers that may stem from the use of marihuana is that it might lead to addiction to the more vicious narcotics such as heroin.

The complete pharmacologic and chemotherapeutic studies are in the report. Loewe (1945) confirmed that the principal site of action of the drug is the brain, and the peripheral effects are negligible. No scientific therapeutic use of marihuana could be established.

Loewe (1945) confirmed that the 2 main pharmacologic responses to cannabis are *motor ataxia* and *corneal areflexia.* These 2 effects appear to be dissociated. Furthermore the psychic response in man shows a parallelism to the ataxia activity but not to the areflexia.

This absence of therapeutic usefulness and the addictive action of cannabis have been repeatedly confirmed. The drug is a vicious one and serves no purpose in therapy.

Cannabis comes within the purview of the Harrison Narcotic Act (1937).

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# 25

# *Central Nervous System Depressants. The Problem of Drug Addiction*

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The problem of addiction to narcotic drugs is an ancient and a serious one. Certain narcotic drugs such as alcohol produce tolerance and habituation, and in many individuals this is a grave malady. Yet the chronic alcoholic, if he has the will to refrain from any type of alcoholic beverage (total abstinence), can overcome the disease. The withdrawal symptoms are not serious; they are mainly psychic. The body does not acquire physical dependence on the presence of alcohol in the tissues. With morphine a different pattern of addiction is presented. As with alcohol the individual shows tolerance and habituation. But further, he develops a definite physical dependence upon the drug. It sometimes occurs that the withdrawal symptoms of morphine addiction are mainly psychic, but after long repeated use of the drug physical dependence develops. The withdrawal of morphine after addiction produces devastating symptoms which are ameliorated by a return to the drug. Therefore, true addiction embraces the three phenomena:

1. Tolerance
2. Habituation
3. Dependence.

Although morphine and other similar analgesics are the drugs which most readily produce addiction under conditions of high dosage levels, other sedative drugs may also be addictive. For example, Isbell (1950) observed withdrawal symptoms similar to *grand mal* convulsions following the cessation of continued high dosage levels of the barbiturates.

**Definitions.** Tatum *et al.* (1929) defined *tolerance* to a drug as *that phenomenon characterized by the fact that more and more of the drug must be used to produce equivalent effects.*

*Habituation* is defined by the same workers as a *condition wherein one becomes accustomed to but not seriously dependent upon a drug.*

*Dependence* is defined by Tatum *et al.* as the *distortion of normal physiologic processes which results from the prolonged administration of addicting drugs and which is manifested by the necessity for the presence of an adequate amount of one of these drugs in the body for the maintenance of physiologic equilibrium.*

*True addiction*, which embraces these three phenomena, is produced by opiates and certain synthetic narcotics. It has been defined as *that condition of mind or body induced by drugging which requires a continuation of that drug, and without which serious physical and/or mental derangement results.*

The World Health Organization (WHO) gives the following definition of drug addiction:

*"Drug addiction is a state of periodic or chronic intoxication, detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:*

1. *An overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;*
2. *A tendency to increase the dose;*
3. *A psychic (psychological) and sometimes a physical dependence on the effects of the drug."*

The phenomenon of addiction therefore is a serious psychosomatic condition in which the individual phenomena of tolerance, habituation, and dependence are intricately combined (Himmelsbach, 1939). Indeed the phenomenon of true addiction may be considered to involve the individual at three levels, all existing within the framework of addiction. The first of these is *psychic*, which has been referred to as habituation. The second is *biochemical*, which embraces the phenomenon of tolerance. The third is *physiologic*, and this involves physical dependence on the drug.

**Tolerance.** The phenomenon of drug tolerance in general was discussed elsewhere (page 43). Tolerance to morphine and similar analgesics presents a special feature of tolerance, a tolerance which is intimately associated with physical dependence. It was believed formerly that tolerance to morphine was dependent, partially at least, upon the acquired capacity of the tissue cells to catabolize greater quantities of morphine. Today this view seems no longer tenable. Woods (1954) demonstrated that the excretion of morphine by tolerant dogs was equal to that amount excreted by the nontolerant animal. Furthermore, an analysis of the tissues of tolerant and nontolerant rats, dogs, and monkeys showed no significant difference in morphine concentrations. It is of special interest that the morphine concentration in the brain during the highest plasma levels was only $10^{-6}$ molar. Besides, 48 hours after the last dose all of the morphine had been eliminated from the brains of tolerant animals. It appears therefore that for an explanation of tolerance to morphine one must look at the effect of the drug upon the target cells in the central nervous system.

It is well established that morphine elicits a biphasic response in the central nervous system. It evokes transient excitation and deep depression. Tatum *et al.* (1929) proposed the "dual hypothesis" of morphine tolerance. These two opposing effects of morphine may be elicited by the contact of the drug with two different cellular loci. Tolerance is acquired resistance to the narcotic effect of morphine. At the same time dependence is acquired to the *cumulative effects, a longer enduring direct excitation.* The effector mechanism responsible for excitation becomes more sensitive to the repeated action of the drug while resistance is acquired to the narcotic effect.

Seevers and Woods (1953) evolved a hypothesis based upon the Tatum concept. They have observed that the primary site of action of morphine is on the internuncial neuron. The axon was found to be the site of vulnerability. They suggest that the predominant narcotic effect of morphine is a cell surface phenomenon, whereas the excitant action is elicited by the intracellular action of the drug. It has been demonstrated that definite structural changes are produced in the brains of monkeys by the acute or chronic administration of morphine. Tolerant animals do not show these structural changes in the brain when the drug is given in doses several times those required to produce the changes in nontolerant animals. The damage affected mainly the white matter of all portions of the cerebral hemispheres. Various degrees of demyelinization take place, which include the breakdown of the myelin sheaths and axis cylinders. These changes are blocked by the action of N-allylnormorphine. These structural changes appear to be concerned with the narcotic action (cell surface) of the drug which is blocked by N-allylnormorphine and is associated with tolerance. Thus tolerance to morphine and similar analgesics appears to be associated with the acquired resistance of the target cells to the action of morphine. This resistance is acquired only to the narcotic and not to the excitatory action of the drug.

Axelrod (1956) proposed an interesting hypothesis with regard to morphine tolerance at an enzyme level. A striking resemblance between the cell receptors for narcotics and the enzymes which N-demethylate these drugs was observed. Both the receptors and the enzymes compete for morphine and its antagonist N-allylnormorphine. Rats were made tolerant to morphine by repeated daily injections. Upon sacrificing the animals and testing the capacity of their livers to N-demethylate morphine, dilaudid, and meperidine, a marked reduction in demethylation activity was observed. When N-allylnormorphine was administered with

morphine the diminution in enzymic activity of the liver was significantly less than with the tolerant animals receiving morphine only. Axelrod suggests that the continuous interaction of the narcotic drugs with the demethylating enzymes causes their inactivation. Furthermore, the continuous interaction of narcotic drugs with their cell receptors may inactivate the receptors with the production of tolerance. It is possible that a diminished response to narcotic drugs may occur as a result of unavailability of receptor sites.

That the drug loses its acute toxicity to the tolerant individual is evidenced by the fact that the famous English opium eater, Thomas De-Quincy, took an amount of laudanum in one day to equal 5 gm. of morphine.

In general clinical practice, tolerance to the analgesic and narcotic effects of morphine appears within 3 weeks of daily administration. Tolerance will develop more rapidly with larger and more frequent dosage. There are, of course, many individual variations to this generalization.

**Habituation** is mainly a psychic phenomenon. It is an adaptation to the repetitious dose of the drug. It is a mental conditioning to the drug effect. Alcohol, caffeine, barbiturates, and other drugs produce habituation. But with these drugs the psychic dependence can be comparatively easily terminated. The opiates, however, produce a strong habituation which appears to be, partially at least, a resultant of physical dependence. It is difficult to dissociate accurately the two phenomena. The basic phenomenon in habituation or emotional dependence is the production of a euphoria in the individual by the use of the drug. Anxieties are relieved and tensions are resolved. The individual seeks to achieve this mental state of tranquility by repeated use of the drug.

In the early stages of addiction, habituation is the principal effect of the drug. This precedes physical dependence and is more easily treated than the physiologic phenomenon of dependence. It is clear, therefore, that in addiction, as in most diseases, the process of rehabilitation is most readily achieved and more likely to be permanent in the early stages of the process.

**Physical dependence.** That true addiction is not merely a psychic phenomenon is evinced by the fact that it occurs in many species of animals and in man may occur *in utero*. Besides, the syndrome is more or less uniform in most individuals. It is predictable.

Evidence definitely points to alteration of the cells of the central nervous system as a prime factor in dependence. The exact nature and the fundamental mechanism of the change are unknown. Under the discussion of tolerance it was pointed out that morphine and similar drugs can produce definite structural changes in the brain. Other tissues may become tolerant to the action of drugs, *but probably only the central nervous system is capable of developing physical dependence.* When drugs like morphine are administered repetitiously so that the dissipation of one group of molecules adsorbed on the appropriate neuronal receptor sites is replaced by another population of drug molecules, a hyperexcitable state is developed in the neuron. This state of drug-induced hyperexcitability can be reduced by satisfying the receptor mechanism of the neuron with another charge of molecules of the drugs. There is no adequate explanation of this phenomenon. It might involve the use of new enzyme pathways of metabolism in which the drug or one of its metabolites has become an essential substrate. Additional drug at the receptor might involve protection against changes of a structural nature in the neuron. Furthermore, it is possible that the presence of the drug causes the distortion of homeostasis for which the brain has over-compensated. The administration of more drug antagonizes the over-compensation, establishing a vicious cycle. Indeed one of the most plausible hypotheses of physical dependence is based upon the last-mentioned distortion of homeostasis.

The hypothalamic centers are concerned with the maintenance of bodily *homeostasis*. Cell hydration, hemoconcentration, blood sugar, body temperature, and many other factors which are responsible for bodily chemical equilibrium are controlled by hypothalamic centers. Morphine distorts this balance. The nervous mechanism, in order to compensate for this imbalance, over-compensates. There is an increased irritability of all reflex centers and strong hemohydration. Possibly this is the result of the over-compensation of the nervous mechanism to maintain homeostasis. Therefore when the drug is withdrawn the individual is left in a state of distorted chemical balance, which the drug will temporarily equilibrate.

The addiction liability of the various narcotic analgesic drugs is given in table 25-1.

**How do people become addicted?** The number of persons who become addicted to narcotic drugs by the legitimate use in the relief of pain is

TABLE 25-1

*Comparative Addiction Liability of Analgesic Drugs**

Vogel *et al.*, 1948

| Drug | Physical Dependence Liability | Habituation Liability | Total |
|---|---|---|---|
| Morphine | 4 | 4 | 8 |
| Dihydromorphinone hydrochloride | 4 | 4 | 8 |
| Metopon | 3 | 4 | 7 |
| Meperidine hydrochloride | 2 | 3 | 5 |
| Methadone | 1 | 4 | 5 |
| Codeine | 2 | 1 | 3 |

* Comparative addiction liability of analgesic drugs. The numeral 4 indicates that the particular drug has the greatest liability of all the drugs with respect to the particular addiction characteristic shown; the numeral 1 indicates the lowest liability; the sum of the 2 characteristics gives the total addiction liability, the highest possible addiction liability score being 8 and the lowest 0.

comparatively small. Addiction to drugs may result from a dose given by one addict to another individual and repeated. It may be taken as the result of a dare. Then, too, the drug produces a euphoria, an escape from reality, and may be first taken to achieve this escape to a subcortical level of existence. Others in middle life may take opiates to suppress an anxiety neurosis that troubles them, when in retrospect they view the gap in their lives which separates ambition and achievement.

One is alarmed by the large number of youthful addicts to heroin today. Many of these individuals are initiated by the smoking of marihuana cigarettes. Ultimately this type of indulgence no longer produces the "kick" or "boost", and they take recourse to more powerful and truly addictive drugs like heroin.

Laskowitz (1961) in his studies of the adolescent addict concluded that he is socially distant, suffers from a feeling of inadequacy, lacks courage, and desires to be shielded and pampered. He harbors a "private logic" that many of the laws and moral restraints do not apply to him. He shows marked character deviations in social relationships and sex and his occupational efforts are usually pathetic.

Owing to the recent increase in narcotic addiction among young adults, the treatment of infants born to mothers addicted to narcotics poses an important medical problem. Kunstadter *et al.* (1958) encountered 5 such cases in a 3-year period in the Michael Reese Hospital in Chicago. It has been long recognized that mortality and morbidity rates among these infants are high. They are frequently immaturely born and exhibit withdrawal symptoms. Predominantly these symptoms are *hyperactivity*, *trembling*, and *twitchings or convulsions*, along with a *shrill high-pitched, prolonged cry*. *Hunger* is usually persistent. Treatment generally consists of the administration of diminishing doses of barbiturates, oxygen inhalation, and antibiotics for respiratory distress. Electrolyte balance and fluid balance must be carefully considered.

**Types of people who become addicted.** Statistically it may be stated that in the United States about 80 per cent of drug addicts are male, 56 per cent are Negroes, and many of the addicts have a criminal record. Furthermore, it has been established that this problem is associated with life in congested urban centers. For example, of the approximately 50,000 addicts in the United States, 47 per cent are in New York, 15 per cent in Illinois, 16 per cent in California, and the other states harbor the remainder of the addicts. In these three states the addiction is concentrated in the large cities. Nevertheless, addiction may occur in any environment; the individual may come from any stratum of life.

The number of persons who become addicted from the use of narcotics prescribed by physicians for the relief of severe pain is comparatively small. The percentage of accidentally addicted estimated by Rayport (1954) was about 14 per cent in more than 1000 cases. This points to the fact that the basic psychic pattern of the person plays a dominant role in addiction liability.

It is estimated that approximately one-third of the addicts owe their addiction, in part at least, to over-indulgence in alcohol. In these individuals the same basic personality defect which prompts the use of alcohol as an escape from reality is likely also to be responsible for their taking recourse to narcotic drugs.

Since about three-quarters of the addicts are first criminals, it does appear that we are dealing with persons with a definite psychopathic diathesis. These are individuals who have misinterpreted their environmental settings and their place in the social order, and have attempted to mask the impact of reality by the effect of narcotic drugs.

**Incidence of addiction.** The incidence of addiction is difficult to establish with the degree of certainty with which it is established with other diseases. In many cases where the symptoms are not severe it may go on for years unknown to anyone but the addict. The ever-increasing rigid enforcement of the Harrison Act under the able leadership of Commissioner H. J. Anslinger and his successor Henry L. Giordano has forced the illicit market in this country to depend on quantities of narcotics (usually heroin) that may be smuggled or unlawfully introduced into the United States from abroad as its principal supply. The Bureau of Narcotics cooperated with many foreign countries in assisting them to curtail foreign sources of supply and has been successful in eliminating some important sources of heroin which were feeding the illicit traffic in the United States. At present the main sources of heroin are Europe, Near East, Mexico, and Communist China. There is also some smuggling of opium from Mexico, India and Singapore. Some diversion of narcotics from legitimate medical channels is noted, by means of forgery of prescriptions, obtaining prescriptions from physicians through fraud and misrepresentation, or by theft from or robbery of drug stores, hospitals, and physicians' offices and bags.

It now appears since the going down of the Iron and Bamboo Curtains that the traffic in illicit opium is increasing. The U.S.S.R. does not submit complete reports on illicit traffic in narcotic drugs. It is estimated that the world's annual production is about 6500 tons; medical needs are 1000 tons. It is reported that as much as 4000 tons are produced in Red China, which is the major source of illicit narcotics in the world.

The number of addicts in the United States in 1924 was estimated to be 1 in every 1000 of the general population. In 1937, after a careful survey, the incidence was 1 in every 3000 of the general population. In 1961 it was 1 in every 4000. During World War I there was 1 rejection for drug addiction in every 1500 men processed for the armed services. In World War II, in the male age group of 18 to 38, there was only 1 rejection in every 10,000 men processed for the armed services. This same rate of addiction holds true in Canada.

A post-World War II increase in addiction, particularly among the youth, took place in certain neighborhoods, and in certain segments of the population in some of the larger cities of the country, but by the end of 1952 this problem had been brought under control.

**Drug addiction in the United States.** According to "Traffic in Opium and Other Dangerous Drugs," Bureau of Narcotics publication, the estimated total number of narcotic addicts in the United States for the year ending December 31, 1961, was between 45,000 and 50,000, or an incidence of about 1 in 4000 of the population. Estimates reflect that 94 per cent used heroin, 2 per cent used morphine, and most of the remaining 4 per cent used synthetic drugs, opium, paregoric, or codeine.

Included in the total number of addicts enumerated in the Bureau of Narcotics survey of addiction begun in 1953, are more than 12,000 who have remained active throughout the 8-year period 1954 through 1961. Users of marihuana and cocaine have been excluded in this survey.

The ethnic distribution of narcotic addicts in the United States is shown by figure 25-1 of the Federal Bureau of Narcotics.

Since World War II the incidence of addiction among persons under 25 years old has increased greatly. A very large segment of the patients in the government narcotic addict rehabilitation hospitals today is composed of young adults.

In Great Britain, the authorities reported between 800 to 1000 drug addicts "known to the authorities." No estimates have been made. This figure includes mostly doctors and nurses whose addiction was discovered during inspections of hospital records or during inspections of physicians' records.

There has been a great deal of study devoted to the comparison of narcotic control in the United States and Great Britain. It appears that the British law is more lenient in allowing the medical profession to supply narcotics to addicts on an ambulatory basis to satisfy their craving. Their problem of addiction is not as great as that in America and appears to be fraught with less criminal violence. Larimore and Brill (1962) studied the problem in England and the United States, considering the epidemiologic factors of addiction. Their conclusions are most revealing and serve to indicate why the British system would probably not be equally efficacious in America. They hold the view that the success of the English system stems from the relative small incidence of "susceptible hosts" rather than from the method of handling narcotics. England enjoys a comparatively homogeneous population. There

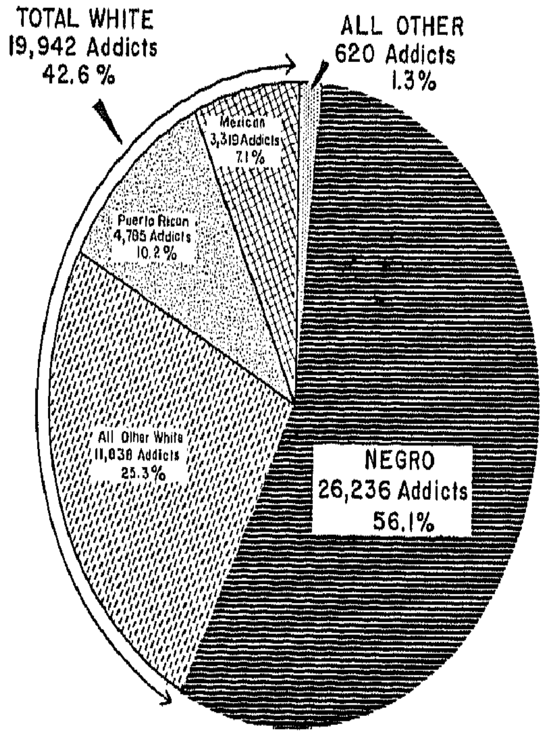

FIG. 25-1. Active narcotic addicts reported in the United States as of December 31, 1961. Total active addicts, 46,798.

are no minority groups subject to the stresses and tensions comparable to those in the United States. The British population also enjoys a lower cultural susceptibility to drug addiction. These statements are of special interest when one considers them in light of the ethnic distribution of addicts in the United States (fig. 25-1).

**Diagnosis of addiction.** Addiction is not always easy to diagnose. As has been stated, many addicts carry on their normal activities without physical or mental signs of their drug addiction. The pinpoint constriction of the pupil is usually a faithful criterion. However, it fails in some addicts. As a rule the addict suffers with chronic constipation, interrupted intermittently by intestinal cramps and diarrhea. Injection depots may be visible on the body. These may have become infected, and abscess formation may be present. They will appear usually on the body in areas especially accessible to the individual with his needle and syringe.

Upon injection of morphine into the addict the response is not one of depression, sedation, and narcosis. He does not respond in the usual manner to the injection of the drug. The drug addict is generally a mendacious individual. Therefore, despite his history and possible physical signs, the most reliable diagnosis for addiction is the appearance of the withdrawal syndrome upon complete and enforced abstinence. The withdrawal syndrome may be induced precipitously upon the injection of nalorphine, page 391.

**Symptoms of addiction.** Light and Torrance (1929) made extensive studies on approximately 100 addicts. They made complete physical examinations, blood studies, basal metabolism, dextrose tolerance, epinephrine response, and other functional activity tests.

They found the heart rate slightly below normal. There was a tendency toward a diminished cardiac size among the addicts. The red cell count was lower and the leukocyte count higher than normal. Blood cholesterol was higher and phosphate lower. There was a uniformity in the *finding of a high blood lactic acid content.* Seventeen per cent of the cases showed proteinuria. There was a lag in the return of the blood-sugar curve to normal after the ingestion of dextrose.

As to the mental changes which occur under opiate addiction, opinions are greatly at variance. Many individuals carry on normal mental activity after years of addiction. Besides, it is difficult to dissociate a pre-existing psychotic state from the effects of the drug. Furthermore, the advent of withdrawal symptoms upon abstinence may befog the issue. Rosenfeld (1928) holds the view that not all addicts show psychic disturbances. The period of addiction and the amount of drug used are determining factors.

Addiction is a form of mental bondage. Therefore the addict's will is often in conflict with his disease. He generally becomes an individual of marked indecision. This obtains with most voluntary acts with the exception of the acquisition of the drug.

**Subjective symptoms of addiction.** The opiates produce a euphoria, a sense of well-being which is psychic and not the resultant of a well equilibrated homeostasis. The withdrawal of the drug produces a *dysphoria*, for which the drug partially compensates. Debove (1899) states, "The primary injections of the drug are very disagreeable, being often followed by nausea and vomiting. Then exultation is paramount. This period lasts many weeks or months. Sooner or later no result is obtained from the injections except cessation of desire for the drug. . . . Psychic changes are common. Hallucinations occur and even paranoia." Wikler (1952) described the effect of the intravenous injection of morphine into post-addicts. Within a few minutes after injection the subject reported a thrilling sensation similar to orgasm. The location of the stimulus was reported as abdominal rather than genital. Following the "thrill" the individual felt "fixed." This term implies a state of satisfaction in which hunger, pain, and sexual desire are abolished. The subject then "goes on the nod" which is a condition of extreme imperturbability and somnolent passivity.

The difficulty of abstinence arises in part from the fact that the addict never forgets the former periods of exaltation, as Seevers expressed it, "the honeymoon of his addiction."

DeQuincy's language regarding this is eloquent and fitting. "The town of Liverpool represented the earth, with its sorrows and graves left behind. . . . Oh! just, subtle, mighty opium! that to the hearts of the poor and the rich alike, for the wounds that will never heal, and for the pangs that tempt the spirit to rebel, bringest an assuaging balm; eloquent opium . . . which brings a brief oblivion to the wrongs unredressed and insults unavenged."

DeQuincy held the view that every event which registers in the cerebral cortex of man makes an indelible impression. Opium pushes away the veil which obscures these happenings from memory.

Heroin addiction continues to produce a euphoria in the addict, and the cessation of its use therefore becomes more difficult. Morphine is required by the addict to restore him to a false sense of normalcy. The craving for this pseudonormalcy is difficult to overcome.

**Withdrawal symptoms.** Himmelsbach (1939) has observed and listed withdrawal symptoms as they occur in man. He selected some of the easily discernible objective symptoms and devised a quantitative method for their scoring. These signs of dependence are listed in the approximate order of their appearance following withdrawal. They are grouped according to their significance in evaluating the severity of the abstinence syndrome.

ABSTINENCE SYNDROME

| *Mild* | *Marked* |
|---|---|
| Yawning | Rise in temperature |
| Lacrimation | Increase in respiratory rate |
| Rhinorrhea | Increase in systolic blood pressure |
| Perspiration | Restlessness |
| | Insomnia |
| *Moderate* | *Severe* |
| Tremors | Vomiting |
| Gooseflesh | Diarrhea |
| Anorexia | Weight loss |
| Mydriasis | |

Withdrawal symptoms begin about 8 hours after abstinence, reach a peak in 40 hours, and their subsidence begins in about 10 days. When an addict is stabilized on morphine, for example, 60 mg. 4 times a day, Wikler (1952) showed that the abstinence syndrome could be immediately induced by a subcutaneous injection of 15 mg. of N-allylnormorphine. This morphine derivative antagonizes the narcotic action of morphine and appears precipitously to cause the withdrawal syndrome in the addict.

**Treatment of addiction.** Treatment of addiction to opiates is a difficult and painstaking problem. Many opportunities for controlled studies have been provided in the United States Public Health Service Hospitals in Lexington, Kentucky, and Fort Worth, Texas. These hospitals are maintained expressly for the purpose of rehabilitating addicts and simultaneously elucidating by pharmacologic research the entire problem of addiction. Their task has been performed with a high degree of excellence.

Despite the most advanced methods of psychotherapy, occupational therapy, and drugs to combat addiction, success has not been remarkable. From 1936 to 1941, 4700 addicts dismissed from the hospitals have been reviewed. Only 25 per cent remained abstinent. Seventy-five per cent of this number took recourse again to opiate medication. The 1948 surveys indicate that about 20 per cent of the addicts remained abstinent over a 7-year period.

Since 1948 the California State Board of Medical Examiners has achieved remarkable results in rehabilitating addicted physicians. About 92 per cent of the physicians placed on probation for the purpose of treatment and rehabilitation have not returned to abusive use of narcotic drugs.

The program in Alameda County, California, is worthy of special comment. The N-allylnormorphine test for narcotic addicts who are on probation or parole is obligatory to determine whether or not total abstinence is in effect. The success of the program is evinced by the fact that of 739 persons brought to the test by way of arrest 38 per cent were positive. On the other hand, of 3000 tests given to probationers, less than 5 per cent were positive. Significant is the fact that addict associated crimes, such as auto-burglaries and prostitution dropped significantly since the use of the N-allylnormorphine test.

The narcotic may be withdrawn at once or gradually over a period of 2 or 3 weeks. Placebos may be substituted for the drug for a short period of time. Scopolamine, chloral hydrate, amobarbital sodium, and bromides have been used as substitutes for the opiate which has been withdrawn. Undoubtedly these drugs merit consideration during the stage of acute withdrawal symptoms. The hypnotics enable the patient to sleep and make the period of anxiety more bearable.

Methadone has developed into a very important substitute therapeutic agent in the treatment of morphine addiction. The withdrawal following methadone addiction is not so severe as with morphine. Generally 1 mg. of methadone is administered for each 4 to 8 mg. of the opiate which had been used. After about a week rapid withdrawal from methadone is instituted. The withdrawal syndrome from methadone is comparatively mild.

After the achieving of withdrawal, occupational therapy is especially useful. The patient must be kept occupied. In the Lexington hospital rug weaving, cabinet making, and tasks providing a combination of mental activity and manual dexterity are employed.

Psychotherapy must be adequate. The patient must be reassured of his ability to escape permanently from the bondage of addiction. He must be taught the same lesson that the alcoholic must learn—"the all or none principle." Abstinence must be complete, and to achieve it all other pursuits in life are of secondary consideration. Follow-up care for the patient for months or even years after hospital discharge is essential.

The enlistment of the help of all of the agencies available in the patient's environment is necessary to assist him in coping with life's difficulties rather than seeking escape by again taking recourse to drugs.

As a result of a joint study by the National Research Council and the American Medical Association, it was concluded to oppose ambulatory treatment plans (1962).

"These two organizations support (1) after complete withdrawal, follow-up treatment for addicts, including that available at rehabilitation centers, (2) measures designed to permit the compulsory civil commitment of drug addicts for treatment in a drug-free environment, (3) the advancement of methods and measures towards rehabilitation of the addict under continuing civil commitment, (4) the development of research designed to gain new knowledge about the prevention of drug addiction and the treatment of addicted persons, and (5) the dissemination of factual information on narcotic addiction."

The comparative hopelessness of our modern methods of treating addiction to opiates should stand always as a clarion signal to the young physician. The incidence of addiction among the medical profession is many times greater than among the general population. That availability and propinquity play important roles is obvious. But in addition, the physician is constantly living in and sharing the emergencies and exigencies of other people. To escape the emotional trauma the opiate is used instead of a good vacation. You cannot win against it. Morphine is the Dr. Jekyl and Mr. Hyde of medicine. The best cure for addiction is never to let it happen.

Bloomquist (1960) states the problem of the physician's becoming an addict in cogent and colorful language. "There it is, within your reach—release from stress and strain, from trouble and pain. No long arm of the law to stop you—not right away, anyway. No fear of running out of supply, of having to steal the stuff. The key that unlocks all this euphoria is your own prescription blank. Ninety-nine physicians are able to see the bomb in this inviting booby trap. In their respect for the evil as well as the good in narcotics, they gingerly step aside to prevent the explosion. But the hundredth doctor? He becomes the addict. Both he and his practice are blasted. Sometimes the pieces can be put together again."

### The Physician's Responsibility under the Harrison Narcotic Act

The following items of special interest to the physician point out his responsibility under the Harrison Narcotic Act. These were taken from a statement of the former Commissioner of Narcotics H. J. Anslinger (1959).

*Registration.* (a) *Qualifications prerequisite.* A physician who intends to practice medicine and to administer or dispense narcotic drugs in the course of such practice must apply for registration under the Harrison Law with the Director of Internal Revenue of the district in which he proposes to practice (using form 678 obtainable from the Director) and must pay the appropriate occupational tax for the fiscal year applicable. Before being entitled to such registration, however, he must be lawfully entitled under the laws of the state or territory or district wherein he intends to practice, to distribute, dispense, give away, or administer narcotic drugs to patients upon whom he, in the course of his professional practice, is in attendance. In the case of a medical practitioner, this requirement usually means that the applicant is a physician who holds an unrevoked and unrestricted license to practice medicine in the particular state, territory or district. To be entitled to registration, however, in the case of any type of practitioner of the healing art, it must appear that he is entitled under the State laws to distribute, administer, or dispense narcotic drugs to patients whom he is professionally attending. "The right to register and pay tax under the Federal statute depends on the right to dispense under the State laws."

(b) *Inventory required.* Every person making application for registry or re-registry as a physisian shall, as of December 31 preceding the date of his application or any date between December 31 and the date of application for such registry or re-registry, prepare in duplicate an inventory of all narcotic drugs and preparations on hand at the time of making such inventory. The inventories shall be prepared on the reverse side of form 678 (the form of application for registry or re-registry obtainable from the Director of Internal Revenue). The original of the inventory, therefore, is a part of the application for registry or re-registry which is sent to the Director of Internal Revenue; the duplicate copy of the inventory must be kept on file by the maker for a period of two years.

*Dispensing and prescribing—in general.* (a) *Direct dispensing or administration.* A physician may obtain narcotic drugs for direct dispensing or administration to patients only on official order forms. He may not obtain narcotic drugs on a so-called prescription for general office use. Official order forms are obtainable from the Director of Internal Revenue in a book of ten sets (each set consisting of three copies, an original, triplicate, and duplicate, with interleaved carbons). The form is to be prepared in triplicate and signed by the physician, the original and triplicate copies being forwarded to a qualified manufacturer or wholesaler, and the duplicate copy being retained by the physician for a period of two years subject to inspection by a duly authorized Federal or State narcotic officer. The order form may be prepared in typewriting, ink, or indelible pencil, but not by the use of an ordinary lead pencil.

(b) *Prescribing.* A physician may issue for a bona fide patient, for medical purposes only, a prescription for narcotic drugs which may be filled by a qualified retail dealer (druggist).

*Prescriptions.* (a) *Formal requirements.* A prescription for narcotic drugs shall be dated as of and signed on the date when issued and shall bear the full name and address of the patient and the name, address and registry number of the practitioner. A physician may sign a prescription in the same manner as he would sign a check or legal document, as, for instance J. H. Smith, John H. Smith, or John Henry Smith. Prescriptions should be written with ink or indelible pencil or typewriter; if typewritten, they should be signed by the practitioner. The refilling of a prescription for taxable narcotic drugs is prohibited.

(b) *Misuse of prescription form as an order form.* A physician must not use his prescription form to obtain narcotic drugs for general office practice. Narcotic drugs desired for general office practice are obtainable on official order form, as above described, from a qualified manufacturer or wholesale dealer. An order for narcotic drugs for general office practice, written on a prescription blank, is not a lawful prescription within the meaning of the law and can have no effect to validate the sale which is illegal.

*Ambulatory treatment for drug addition.* The ambulatory treatment for the cure of drug addiction has always been disapproved by the United States Bureau of Narcotics because its observation and experience have shown that the object of the treatment is practically never achieved. The average drug addict who purports to undergo this treatment will invariably seek other sources of supply as his dosage is reduced.

*Recognized (institutional) treatment.* The most practical plan of applying the only proper and scientific method of treating narcotic drug addiction under the conditions laid down by the Com-

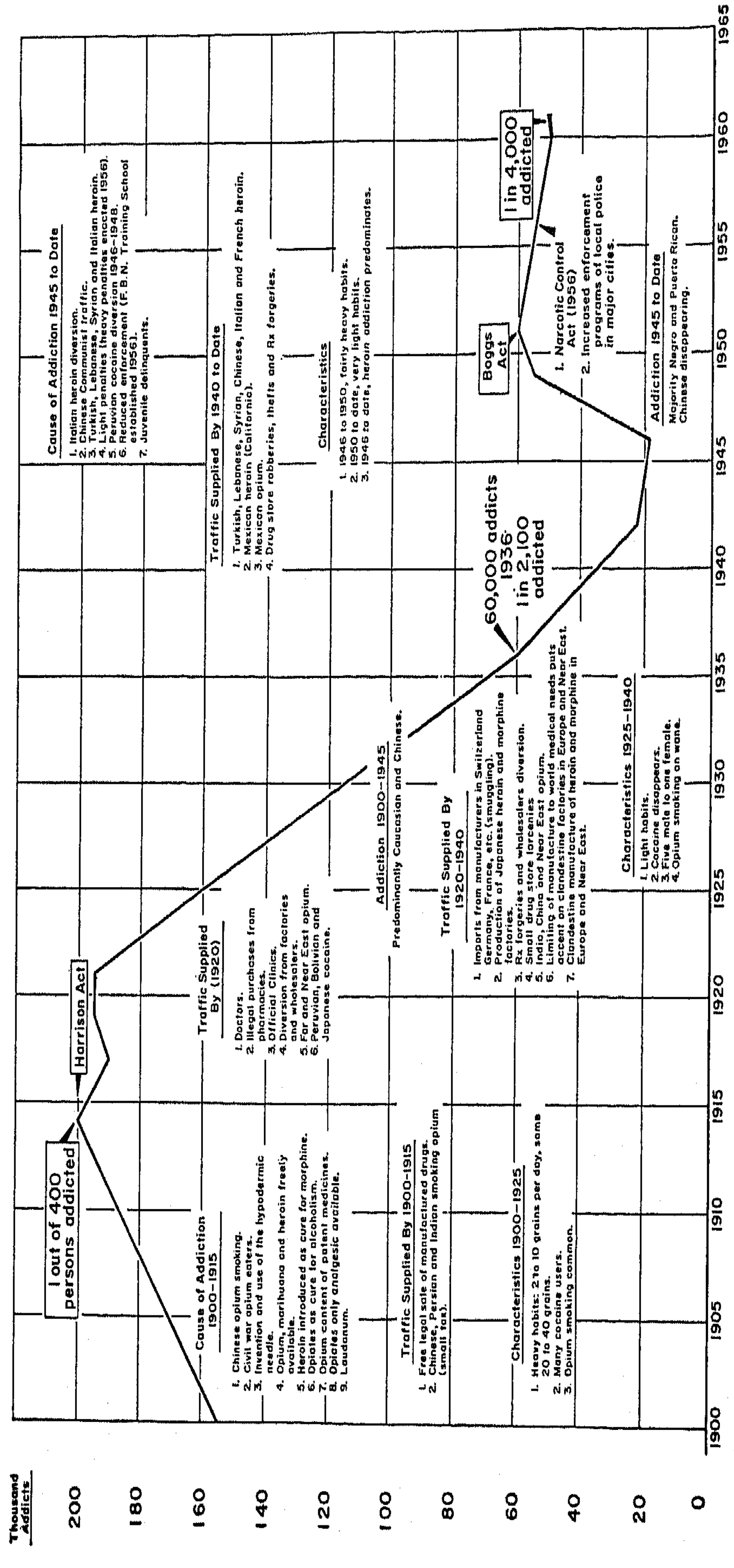

FIG. 25-2. History of narcotic addiction in the United States

mittee on Narcotic Drugs of the Council on Health and Public Instruction and reaffirmed in 1957 by the Council on Mental Health, is to establish an institution properly staffed and equipped for the purpose. By the Act of Congress approved January 19, 1929, provision was made for, and there were later constructed and put in operation, two institutions located at Lexington, Kentucky, and Fort Worth, Texas, respectively, for the treatment and rehabilitation of narcotic drug addicts, under the supervision of the United States Public Health Service. The facilities of these two institutions, available primarily for prisoner-addicts, are also made available for voluntary applicants, even if they are unable to pay a nominal sum representing part of the cost of the treatment. A large number of drug addicts, including some physicians, have received treatment and rehabilitation in these institutions.

The Federal Narcotic Law was amended in 1957 to allow the filling and dispensing of certain narcotic preparations on verbal request from a registered physician, provided the preparation meets certain specified requirements. Responsibility for compliance with these requirements rests upon the pharmacist. Under these new provisions, for example, *certain codeine compounds* may be prescribed by oral prescription up to 1 grain (64 mg.) codeine content per tablet, capsule or other dosage unit and in liquid preparations containing not more than 8 grains (518 mg.) per fluid ounce (30 ml.) certain compounds of dihydrocodeine, dihydrocodeinone, dihydrohydroxycodeinone and ethylmorphine not to exceed specified strengths are also permissible on oral prescription under these regulations. Apomorphine, N-allylnormorphine, papaverine, and narcotine may also be so prescribed either as such or compounded with other drugs.

In September 1962, a White House Conference on Narcotic and Drug Abuse, held in Washington, D. C., devoted much time to discussion of hospital treatment and aftercare of narcotic addicts.

The Narcotics Manufacturing Act of 1960 provides for the licensing of manufacturers of synthetic and natural drugs and for the establishment of manufacturing quotas for all basic classes of narcotic drugs, thus limiting production of those drugs to only the quantity needed for legitimate medical and scientific purposes.

Figure 25-2 shows graphically the progress which has been made in the United States in curbing narcotic addiction through the mechanism of rigid law enforcement and the cooperation of the members of the health profession. We can be proud of the record; let us attempt to improve it for the future.

The authors have frequently heard Commissioner Anslinger, speaking to medical students, say, "Gentlemen, if you do your duty conscientiously as dictated to you by the ethics of your profession, you will have no need to fear the law."

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# 26

# *Central Nervous System Depressants. The Barbiturates*

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Chemical agents are capable of influencing sleep or wakefulness. Substances that facilitate sleep are referred to as *hypnotics*, *somnifacients*, or *soporifics*. To this class belong the barbiturates. Those agents that act to produce wakefulness are known as *stimulants*. These drugs are useful in evoking mild cerebral stimulation and *mood elevation*. They are also valuable in pathologic sleep states such as narcolepsy.

Natural sleep can be readily distinguished from the sleep-like states of coma, trance, and anesthesia in that the ability to be easily aroused is still preserved. Sleep (similar to natural sleep) can be induced by various chemical agents. Therefore certain characteristics of natural sleep will be considered.

**Natural sleep.** Natural sleep is characterized by an almost, although not complete, absence of movement, and what little remains is usually stereotyped and not dependent on critical cortical activity. Grimaces are preserved and may be evoked by lightly stimulating the face of the sleeper. Righting and scratch reflexes are absent, and tendon reflexes diminish or disappear, depending upon the depth of sleep. Muscular relaxation, although never complete, is an important concomitant of natural sleep. There occurs a progressive diminution of action potentials. The condition of the extrinsic and intrinsic muscles of the eye is important because of the role ocular symptoms play in pathologic sleep. The position of the eyes in man found most often during normal sleep is an outward divergence, and the least frequent are divergence downward or convergence upward. However, rotational movement of the eyes may occur in all directions. *The pupils are constricted.* This condition, together with the outward divergence, is considered as representing the "resting state" and probably results from a withdrawal of influences from the central nervous system.

The character of the electroencephalogram (EEG) depends on the depth of sleep. In general, the alpha waves (9 to 11 per second) and beta waves (faster activity) gradually diminish and disappear with the more frequent occurrence of irregular, slow, large voltage delta waves.

The increase in $CO_2$ in the blood and alveoli and concomitant change in blood pH indicate a lowered irritability of the respiratory center. The heart rate slows markedly and the blood pressure falls, but the slowest pulse is found during the second half of the night and the lowest pressure during the first half.

Heat production decreases during sleep, largely owing to the lowered body temperature and to muscle relaxation. Most visceral activities are unaffected and nearly all changes in blood composition and character and volume of the urine can be related to some concomitant of sleep.

**The quality of sleep.** There are many opinions as to what constitutes sound sleep. Most of them are based on pure fancy. The quality of sleep cannot be judged on any one characteristic. There is a great variation in the *duration* of sleep found in a given age group, as well as in the same individual from time to time. However, it may be said that there occurs a gradual decrease in the length of sleep periods with advancing age. The amount of *motility* during sleep also varies. Normal persons change their position often during a night's sleep. This type of movement occurs more frequently during the second half of the night. The *depth* of sleep is usually determined by the threshold of auditory sensitivity. The depth of sleep curves so obtained show several curves of varying magnitudes and intensities which usually become shallower and shorter during the second half of the night. Evidence based on the electrical activity of the brain indicates that dreams occur only during light or partial sleep and are probably a result of activity in certain areas of the cortex (Loomis *et al.*, 1937).

**The effect of sleep loss.** With the exceptions of the effect on the electrical activity of the brain and the psychologic disturbances, very few other significant physiologic, psychomotor, or biochemical changes are found to occur during experimental deprivation of sleep for periods up to 112 hours. Heavy work capacity, psychomotor skills (provided the tests do not require sustained attention), blood sugar, alkaline reserve, hemoglobin, red and white cell count, body weight, basal metabolism, and body temperature show little variation from the normal. Even the urinary excretion of 17-ketosteroids is little affected by such stress and the slight change that occurs is a decrease rather than an increase (Tyler, 1955).

The changes in the EEG begin between 36 and 50 hours of wakefulness and are characterized principally by an increase in the time occupied by waves of higher frequencies. Also a mental multiplication problem which causes an increase in the electrical activity of the brain of the normal rested subject produces little or no increase in the rate in the sleepless man.

Psychoneurotic, schizophrenic, and paranoid-like reactions occur usually after 40 hours of sleep deprivation. In most subjects the symptoms are mild; in a few the reactions are severe, resembling acute schizophrenia of the paranoid type. However, in all subjects normal behavior is restored after a sound sleep. It appears that the mental symptoms produced by sleep loss resemble in many ways the state found in the toxic type of psychosis, particularly those reactions coincident to certain illnesses or over-dosages of narcotic drugs. Usually in the latter type the mental symptoms subside as the patient recovers from his illness or as the drug is eliminated. That the psychologic disturbances occurring during sleep loss may be due to the elaboration or depletion of some functional metabolite is indeed a possibility (Tyler, 1955).

**Theories of sleep.** That sleep is not solely dependent upon the cortex is apparent from the observation that decorticate animals show alternating periods of sleep and wakefulness. Furthermore, there is evidence for the participation of the *hypothalamus in the regulation of sleep and wakefulness.* Mauthner (1890), during the course of an epidemic of sleeping sickness, definitely related the condition to inflammatory lesions in the periventricular gray matter of the brain.

Some investigators believe that sleep results from a depression of activity of the hypothalamus. They maintain that the centers are concerned with keeping man awake. Others hold that sleep results from excitation of these areas. Several chemical theories of sleep have been proposed postulating the production during wakefulness of various "fatigue substances" which depress the activity of the cortex. The evidence offered in support of such "humoral" theories is far from convincing. Pavlov concluded, as a result of studies on the behavior of dogs during experiments on conditioned reflex activity, that sleep is a result of a spread of internal inhibition over the cortex with the eventual involvement of subcortical areas. Kleitman, on the other hand, proposed an "evolutionary" theory of sleep based on the idea that the state of wakefulness is maintained through activity of the hypothalamus. His theory attempts to explain the development of a sleep-wakefulness rhythm from a purely subcortical or primitive one to the more advanced type exhibited by adult man.

Recent investigations have demonstrated that the reticular formation is definitely involved in the states of sleep and wakefulness. It serves as a kind of reinforcing or background function to the central nervous system, augmenting reflex and voluntary movements to a state of maximal facility. In sleep, deactivation of the reticular formation prevails. The deactivation may be *passive*, resulting from the absence of the constant stream of stimuli—humoral, introceptive, extroceptive, and cortical in origin. It may be *active* deactivation also, resulting from tonic and phasic effects produced by the cortex and medulla. It has been suggested that sleep may be the result of passive and active deactivation of the reticular formation (Dumont-Tye and Dell, 1962). The reticular formation is drug vulnerable; it is deactivated by hypnotic drugs.

It is apparent that the physiologic mechanism responsible for sleep is not clearly understood. Until the basic concepts of the physiologic and biochemical aspects of sleep have been clarified, it is doubtful whether an adequate explanation of the action of hypnotics can be achieved. Many efforts have been made to explore the effects of hypnotics on the enzyme systems of the brain. However, the information is fragmentary and difficult to correlate with our present physiologic knowledge of sleep.

## The Barbiturates

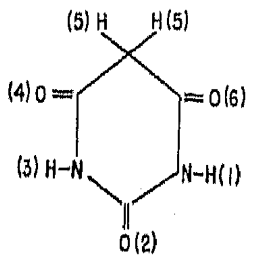
**Historical introduction.** The barbiturates are one of the most important classes of sedatives of the central nervous system. Barbituric acid is malonylurea. It was prepared by Conrad and Gutzeit in 1882. About 20 years later Pokotilo (1907), Fischer and Hoppe (1909), and Fischer and von Mering (1904) prepared diethyl barbituric acid and found that it possessed hypnotic activity. It is said that Fischer named the drug *Veronal* from the Latin "vera" because he believed it to be the "true" hypnotic. Baeyer named malonylurea *barbituric acid*, for he considered it a "key" to a series of compounds. He therefore used a part of the German word "Schlüsselbart", meaning the bit or beard of the key. Others contend that the name was selected because it was prepared on Saint Barbara's Feast Day.

Diethyl barbituric acid was available in this country for nearly a decade as Veronal. It was the sole barbiturate used to any extent in America until *Luminal* or phenobarbital made its appearance shortly before World War I.

After World War I many other derivatives of barbituric acid were synthesized, and the wider aspects of barbiturate therapy were investigated. Short-acting and long-acting barbiturates were synthesized. Intravenous therapy with the sodium salts of the barbiturates began in America shortly after Shonle and Moment synthesized amobarbital in 1923. Many other compounds were made for intravenous therapy in this series, which ultimately resulted in the use of the thiobarbiturate, thiopental sodium, as a general anesthetic, page 333.

Widespread medical interest in this class of substances is manifest today. The most frequently-prescribed drugs for central nervous system sedation are the barbiturates.

**Chemotherapeutic considerations.** The barbiturates represent a pyrimidine nucleus resulting from the condensation of malonic acid and urea. The pyrimidine nucleus is shown in the accompanying formula.



Barbituric Acid (malonylurea, the pyrimidine nucleus)

Barbituric acid is devoid of hypnotic activity. It is only when the positions 5,5 have the appropriate substituent alkyl or aryl groups that hypnotic activity is produced by the compound.

The barbiturates used in therapy are prepared by introducing various groups in the 5,5 positions. *In this respect all of them may be considered different forms of the same substance.* The following principles appear to hold with regard to substitution in the pyrimidine nucleus.

1. The total number of carbon atoms in the 2 groups in positions 5,5 must be not less than 4 or more than 8 for the optimal therapeutic results.
2. Only one of the substituent groups at positions 5,5 may be a closed chain.
3. Double bonds in the alkyl substituent groups produce compounds more readily vulnerable to tissue oxidation. Hence they are short acting.
4. Short chains in positions 5,5 resist oxidation

and are long acting. Long chains are readily oxidized and produce short-acting barbiturates.

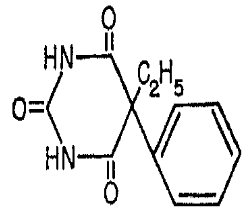
5. The replacement of the carbonyl oxygen atom at position "2" by a sulfur atom produces thiobarbiturates. These are readily detoxified and short acting.
6. The replacement of the carbonyl oxygen atom in position "2" by an HN= group producing a guanidine derivative destroys the hypnotic activity of the molecule.
7. The replacement of the hydrogen atom on positions "1" or "3" by an alkyl group increases the vulnerability of the molecule to oxidation by the tissues.
8. Certain alkyl groups in positions 5,5 will confer convulsive properties upon the molecule. Of this class are 1-3-dimethyl-butyl ethyl barbituric acid and crotyl *n*-butyl thiobarbituric acid.

Clark (1938) estimated that there are 1222 possible barbiturates with no more than 6 carbon atoms in the side chains. About 60 derivatives have been used in therapeutics. Approximately 17 maintain a degree of popularity. Medical practice would not be seriously hampered if this number were reduced to 5 or 6.

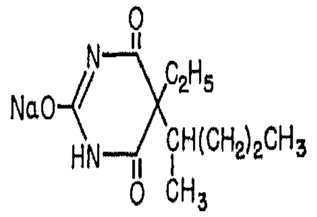
**Solubilizing of the barbiturates.** Barbituric acid and its 5,5 substituted derivatives behave like weak acids. They are capable of uniting with fixed alkalies and forming soluble salts. These salts are hydrolyzed in water, and their solutions are alkaline. Tabern and Shelberg (1933) determined the degree of hydrolysis of several medicinal barbiturates in aqueous solution. They found diethyl barbituric acid sodium 80 per cent hydrolyzed. On the other hand, secondary butyl β-bromallyl barbituric acid sodium was only 11.5 per cent hydrolyzed. Other derivatives were hydrolyzed to degrees lying intermediate between these 2 extremes. The soluble sodium salts of certain barbiturates are shown in the accompanying formulas.

The soluble sodium salts of the barbiturates are used for intravenous therapy. For oral medication they are often preferred owing to the greater dependability of absorption and hence promptness of hypnotic action.

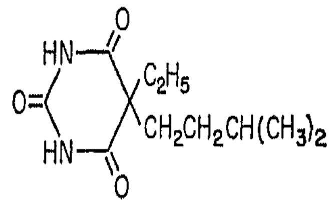
**The generally used barbiturates.** The barbiturates recognized by the U. S. Pharmacopeia are: *phenobarbital (Luminal)*, *amobarbital (Amytal)*, *pentobarbital sodium*, *(Nembutal Sodium)*, *secobarbital sodium (Seconal Sodium)*, *and thiopental sodium (Pentothal Sodium)*. These structures are shown in the following formulas. Other barbiturates in general use are shown in table 26-1.



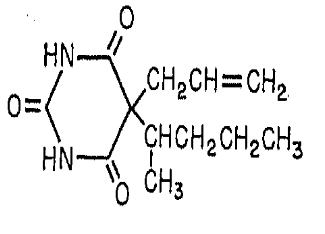
Phenobarbital U.S.P. (Luminal) (phenylethyl barbituric acid)



Pentobarbital Sodium, U.S.P. (Nembutal Sodium) (ethyl-1-methylbutyl barbituric acid sodium)



Amobarbital, U.S.P. (Amytal) (isoamylethyl barbituric acid)



Secobarbital, U.S.P. (Seconal) (allyl-1-methylbutyl barbituric acid)

Production of barbiturates has quadrupled since 1933. It is estimated that a total of 500 tons are manufactured each year. It is claimed that sufficient barbiturate derivatives are now provided to put to sleep 10 million people each night of the year. In 1962 the daily consumption of phenobarbital in America was 0.4 ton.

### THE PHARMACOLOGIC RESPONSE TO THE BARBITURATES

**Barbiturates on the central nervous system.** *The principal response elicited by a barbiturate is depression of the central nervous system.* Depending mainly upon the dose and also upon the method of administration, this depression may be only mild sedation or surgical anesthesia.

TABLE 26-1

*Barbiturates in Clinical Use*

| Duration of Action | Compounds | Substituents | | Other |
|---|---|---|---|---|
| | | $R_1$ | $R_2$ | |
| Long | Barbital | Ethyl | Ethyl | |
| Long | Gemonil | Ethyl | Ethyl | 1-Methyl |
| Long | Mebaral | Ethyl | Phenyl | 1-Methyl |
| Long | Phenobarbital | Ethyl | Phenyl | |
| Intermediate | Alurate | Allyl | Isopropyl | |
| Intermediate | Butisol | Ethyl | 1-Methylpropyl | |
| Intermediate | Dial | Allyl | Allyl | |
| Intermediate | Ipral | Ethyl | Isopropyl | |
| Intermediate | Lotusate | Allyl | sec. Butyl | |
| Intermediate | Medomin | Ethyl | 1-Cyclohepten-1-yl | |
| Intermediate | Neonal | Ethyl | *n*-Butyl | |
| Intermediate | Amytal | Ethyl | Isoamyl | |
| Intermediate | Vinbarbital | Ethyl | 1-Methyl-1-butenyl | |
| Short | Ortal | Ethyl | *n*-Hexyl | |
| Short | Pentobarbital | Ethyl | 1-Methylbutyl | |
| Short | Pernoston | β-Bromallyl | sec. Butyl | |
| Short | Phanodorn | Ethyl | Cyclohexenyl | |
| Short | Sandoptal | Allyl | Isobutyl | |
| Short | Seconal | Allyl | 1-Methylbutyl | |
| Ultrashort | Evipal | Methyl | Cyclohexenyl | 1-Methyl |
| Ultrashort | Pentothal | Ethyl | 1-Methylbutyl | 2-Thio |
| Ultrashort | Surital | Allyl | 1-Methylbutyl | 2-Thio |
| Ultrashort | Brevital | Allyl | 1-Methyl-2-pentynyl | 1-Methyl |

The barbiturates act upon the cerebral cortex. Their effect also likely occurs in the thalamus. Here they interfere with the passage of impulses to the cortex. The effect is manifested on the sensory and motor areas, for the drugs may elicit sleep and also inhibit convulsions. They evoke deactivation of the reticular formation.

When the barbiturates are used orally in therapeutic doses for sedation or hypnosis, their influence upon respiration is slight. Respiration as a rule is very slightly depressed. This is likely due to the general sedation evoked by the drug. Large doses of the barbiturates markedly depress the respiration. When death is caused by these drugs it is the result of respiratory paralysis. Respiratory depression produced by the barbiturates is more marked when they are administered intravenously than when given by mouth. The barbiturates exhibit a wide margin of safety between the dose that embarrasses the respiration and the dose that produces cardiac arrest. Therefore artificial respiration should be employed in barbiturate intoxication.

Cortical oscillograms in monkeys under barbiturate hypnosis resemble those of man in natural sleep. By the administration of larger doses of the barbiturates one can accomplish the complete abolition of the electrical excitability of the motor cortex in the monkey. In this respect the barbiturates are more efficacious than chloral hydrate.

King *et al.* (1957) attribute the effect of barbiturates to a functional block of the ascending influence of the brain stem reticular formation. With increasing doses, however, the barbiturates are capable also of exerting a depressant effect directly upon the thalamic relay nuclei.

Not all patients are uniformly depressed by the barbiturates. An occasional individual may become irritable, restive, and uncooperative after a subhypnotic dose of a short-acting barbiturate. Furthermore, the effective hypnotic dose varies considerably among different patients.

Ramsey and Haag (1946) found that when secobarbital sodium was given orally to mice the lethal dose was considerably lowered when alcohol was given at the same time. The anesthetic dose of thiopental sodium for dogs was also reduced by previous oral administration of 95 per cent alcohol. It therefore appears that the cerebral depressant action of alcohol and the barbiturate is additive. It is our impression that this same additive response to alcohol and the barbiturates prevails also in man and enjoins one to employ with caution the short-acting barbiturates in a patient with a high blood alcoholic content.

Rushton and Steinberg (1963) demonstrated that amphetamine-amobarbital mixtures administered to rats evoked marked stimulation. This was interpreted by these authors as true potentiation of the action of amphetamine by amobarbital.

**Cellular activity of barbiturates in the brain.** It has been demonstrated by many investigators that barbiturates prolong the time required for brain brei to decolorize methylene blue solutions. Jowett and Quastel (1937) showed that barbiturates depress the respiration of brain tissue *in vitro*, and proposed this was due to a blocking effect at a flavoprotein step in the cytochrome chain. Persky *et al.* (1950) provided evidence to indicate that barbiturates attack the dehydrogenase moiety of the pyruvate oxidase complex.

Further investigations in this field have revealed that in brain tissue glucose and pyruvate oxidation is inhibited, but succinate is unaffected. Depression of brain brei respiration is not sufficient to account for the activity of the barbiturates. Indeed certain stimulants to the central nervous system produce this effect. McElroy (1947) proposed that narcotic drugs produced their effect, not by merely depressing the respiratory rate of nerve tissue but by inhibiting some energy-yielding process. This points to the possibility of depression of phosphate bond turnover, thus reducing neuronal activity. Westfall (1951) demonstrated that very small concentrations of barbiturates might indeed increase the rate of respiration of rats' brain slices. Lardy and Elvehjem (1945) suggested that certain agents might accelerate the metabolic rate, but that simultaneously they might decrease the available energy to the tissue by inhibiting phosphorylation. It appears that this is the effect of certain of the barbiturates on brain tissue. Brody and Bain (1954) have shown that several of the commonly used barbiturates inhibited inorganic phosphate uptake of particulate tissue of brain and liver with a pyruvate substrate. For example, with only a 20 to 40 per cent decrease in oxygen uptake caused by thiopental, the inorganic phosphate uptake was almost completely inhibited. Thus the barbiturates appeared to uncouple phosphorylation from oxidation and thereby depress neuronal activity. This activity of the barbiturates on the phosphorylation activity may well play a central role in the depressant effects which they elicit. It has been shown that in hypoglycemic shock both metabolic rate and nervous activity fall equally. However, under thiopental anesthesia nervous activity is abolished with only a slight depression in metabolic activity. Brody and Bain (1953) demonstrated that a number of commonly used barbiturates were capable of uncoupling oxidation from phosphorylation in the mitochondrial preparation of rats' brains. They also observed that a convulsant barbiturate, 1,3-dimethylbutyl ethyl barbiturate, was also active. In addition, Wolpert *et al.* (1956) showed that the hypnotics chloral hydrate and paraldehyde were incapable of uncoupling oxidation from phosphorylation. It follows that the uncoupling action is not essential for hypnotic activity. Therefore one cannot attribute the depressant effects upon the central nervous system of these drugs *in vivo* to this enzymic response *in vitro*. This is likely one facet of their action, coupled with many other enzymic responses not yet revealed. However this newer concept of barbiturate activity appears substantially more adequate than some of the former theories based merely on the over-all depressed oxygen uptake of brain tissue.

Nachmansohn and Wilson (1951) believe that the barbiturates serve as a barrier to acetylcholine synthesis in brain tissue. This may be the result of a block in the synthesis of adenosine triphosphate (ATP) or an interference with the participation of ATP in the reactions leading to the synthesis of acetylcholine. Marks (1956) tested the action of various barbiturates on a "pure" acetylating enzyme system. All of the barbiturates studied inhibited the enzyme system as a function of their respective concentrations. The levels employed were comparable to those achieved when these agents are used for anesthesia. It is of interest that a convulsant barbiturate also produced inhibition. Depressants not containing a urea grouping in the molecule were not effective inhibitors.

The mechanisms of ATP synthesis and acetylcholine formation are mutually dependent. It appears that barbiturates inhibit 2 segments of the chain of chemical events leading to the synthesis of acetylcholine: (1) the formation of

ATP, and (2) the acetylation of choline. These demonstrated enzymic effects of the barbiturates *in vitro* are at present but segments which ultimately must be woven into the complex matrix of neuronal function and consciousness.

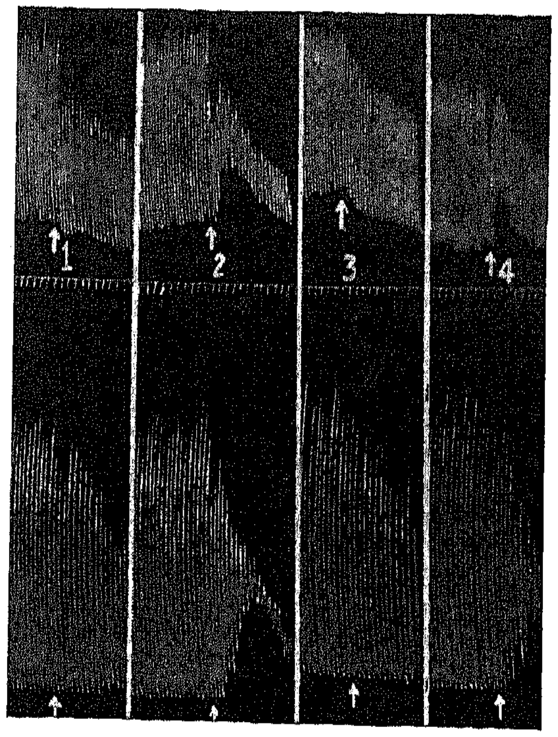


FIG. 26-1. Barbiturates and thiobarbiturates on the rabbit's intestine. Excised longitudinal segments of rabbit intestine. Top record is that of the duodenal segment and the bottom curve is that of the ileal segment. Time in intervals of ten seconds. Tyrode's solution with a pH of 7.6 to 7.8 was used as the bath and oxygenated by bubbling air through it. The concentration of the drug in each case is a 1:20,000 dilution. 1. Thioethamyl sodium. 2. Thiopentobarbital sodium (Pentothal). 3. Sodium pentobarbital. 4. Thiopentobarbital sodium (Pentothal). Pentothal increases the general tonus but decreases the force of the contractions. (*Gruber and Gruber, 1939.*)

**Barbiturates on the circulation.** In oral therapeutic doses sufficient to produce sedation or sleep the *barbiturates do not significantly affect the circulation.* The blood pressure remains normal, and there are no important alterations in the rate, rhythm, or form of the electrocardiogram. In large doses certain barbiturates depress the vagus and hence produce a slightly increased heart rate. Gruber and his associates (1938–1946) studied the effect of various barbiturates upon the heart of the terrapin. The whole heart was exposed to solutions of the drug. They concluded that the barbiturates depressed the cardiovagus peripherally. They behaved alike qualitatively but differed quantitatively. In the compounds studied, Gruber found Ortal sodium, Evipal sodium, pentobarbital sodium, and secobarbital sodium most active on the vagus nerve. The thiobarbiturates do not share this vagal action with the barbiturates. Although these observations are of striking pharmacologic interest, this peripheral vagus activity of the barbiturates is not a problem in clinical medicine when the drugs are used in therapeutic hypnotic doses.

Large doses of barbiturates produce peripheral vasodilatation and a fall in blood pressure. When the drug is metabolized or eliminated the blood pressure returns to normal quite promptly. Exley (1954) studied the action of the commonly used barbiturates on autonomic ganglia. He showed that small intravenous doses in cats produced a transient depression of the sympathetic ganglia. Amobarbital and butabarbital were the most active; the thiobarbiturates were the least active. Exley contends that one of the components in the depressor response of intravenous barbiturates in man is the depression of the vasomotor ganglia. He is of the opinion that this is likely to prevail in patients subjected to the "Amobarbital Sodium Sedation Test."

The constituents of blood are not significantly influenced by therapeutic doses of barbiturates.

Barbiturates have been shown to be bound by plasma albumin during their sojourn in the blood. Goldbaum and Smith (1954) observed an inverse relation between the duration of action and the extent of plasma protein binding. The long-acting barbiturates were found to be bound to a small degree to the plasma proteins, whereas the ultrashort-acting compounds were bound to the greater degree. These findings indicate that plasma protein binding does not interfere with the onset of sedation evoked by the barbiturates.

**Barbiturates on the gastrointestinal tract.** It has been well established that the barbiturates as a class depress intestinal muscle activity. The response is elicited in the intact animals and with smooth muscle preparations. The action of the thiobarbiturates is somewhat different from that of the barbiturates on intestinal smooth musculature. The thiobarbiturates in dilute solution generally increase the tonus but diminish the amplitude of contraction of excised intestinal strips. These effects on the isolated rabbit's intestine are shown in figure 26-1 by Gruber and Gruber (1939).

Many workers in the field of barbiturate pharmacology have emphasized the depressant action of the barbiturates on intestinal musculature.

O'Malley *et al.* (1956) observed that intraperitoneal doses of pentobarbital sodium which produced only mild narcosis in rats delayed the passage of charcoal meal through the intestines to the extent of 21 per cent. The mechanism of this action is not clearly understood. It likely involves several components among which are the central nervous system depressant action, the direct effect upon the intestinal musculature, and perhaps some vagal depression. In the usual therapeutic dose in man the gastroenteric action of the barbiturates appears to be of no significance. Indeed from our observations on people using barbiturates for years, there appears to be no significant effect on the gastrointestinal tract. They do not find the drugs constipating nor do they find that they produce intestinal distress or diarrhea.

**Barbiturates on metabolism.** *The basal metabolic rate is not affected by therapeutic doses of the barbiturates.* With larger doses basal metabolism is depressed. Peoples and Carmichael (1941) measured the effect of Delvinal sodium on the respiratory metabolism of the *rhesus* monkey. They gave 30 to 45 mg./kg. The larger dose produced surgical anesthesia. During this period the basal heat production was 30.46 Cal./sq. M./hour. This was reduced on the average of 20 per cent by the foregoing dosage level of the barbiturate. Large doses of barbiturates intravenously will elicit a transient hyperglycemia.

The sedation produced by the barbiturates in therapeutic doses might result in a slight reduction in body temperature. The reduction is not of clinical significance.

Neither renal function nor hepatic function is impaired by therapeutic doses of the barbiturates.

**The distribution of barbiturates in the body.** The methods of determining barbiturates in tissues have been greatly improved in recent years. Walker *et al.* (1948) developed an excellent quantitative method for the estimation of barbiturates in blood. The method is dependent upon ultraviolet spectrophotometry. The ultraviolet absorption spectra of the various barbituric acid derivatives were determined by Stuckey (1941). Gould and Hine (1949) refined the extraction procedure to the point where samples as small as 1 ml. of blood serum may be extracted directly, without preliminary protein precipitation, and used for analysis. Indeed it appears that the spectrophotometric methods are superseding the older colorimetric methods for the identification and determination of barbiturates in blood and other tissues.

These methods are the tools which have enabled various investigators to determine the distribution of the barbiturates in body tissues. Although the principal site of the action of the barbiturates is the brain, the compounds are not concentrated in this organ. There are no greater quantities found in the brain than in other tissues, and the spinal fluid contains insignificant amounts even after large doses.

Maynert (1952) used radioactive barbital to study the distribution in various portions of the brain. This compound was selected because it is refractory to tissue metabolic processes. His data showed that barbital is not localized in the diencephalon or in any other parts of the brain examined. The distribution was essentially uniform.

Domek *et al.* (1960) used $C^{14}$-labeled phenobarbital to study its distribution in cat's brain. No metabolites of the drug were found in the brain. In time periods shortly after administration uniform distribution of the drug in the brain was observed. The gray matter of the brain of the adult animal was more readily penetrated than the white matter presumably associated with the nature of the lamination of the myelin sheath. The eventual distribution of phenobarbital in the regions of the brain is nearly uniform. These workers suggest that much of the phenobarbital in the brain is bound to protein.

Barbiturates pass from the mother to the fetus *in utero*. The placenta does not serve as a barrier to the barbiturates (Dille, 1934). Fealy (1958) studied 100 newborn infants delivered from mothers who had received pentobarbital sodium. Placental transmission of the barbiturate occurred almost immediately after the intravenous injection of the drug into the mother. The blood of the infants exhibited plasma levels equal to about 74 per cent of the maternal plasma level. The persistence of the drug in the blood continued for about 3 hours. Barbiturates may appear in mother's milk (Mayo and Schlicke, 1942).

**Fate of the barbiturates in the body.** The barbiturates are removed from the body by 2 different mechanisms. They are excreted in the urine by the kidneys unchanged or metabolized by the liver. The distribution and fate of the barbiturates in the body are shown in figure 26-2.

The barbiturates which act for long periods are mainly excreted by the kidneys. In this class are barbital and phenobarbital. Their substituent groups at position 5,5 are resistant to oxidation. As much as 85 per cent of these compounds may be recovered from the urine. The excretion is slow and takes place over several days. Butler (1954) showed that the proportion of phenobarbital eliminated from the plasma in the course of a day was found to lie within the limits of 11 and 23 per cent. Although through the years it was believed that phenobarbital was excreted by the kidney in the urine unchanged, Butler (1954) identified *p*-hydroxy-phenobarbital in human urine. From 20 to 46 per cent of the hydroxy derivative was excreted in a conjugated form. Renal damage retards the excretion of barbiturates. The fate of many of the barbiturates in the body was reviewed by Maynert and van Dyke (1949).

The short-acting barbiturates are metabolized principally by the liver. Other tissues may also participate in the process. In this class are pentobarbital, amobarbital, and secobarbital. These compounds are not recovered from urine when administered in sedative doses. The brevity of the response elicited by these drugs is dependent upon their rapid metabolism in the body. That the liver plays an important role in this metabolism is evidenced by the facts that in animals in which the liver has been damaged by chloroform or in hepatectomized animals, the action of these compounds is prolonged. Germane to this subject are the experiments of Cooper and Brodie (1955) who showed that Evipal (hexobarbital) is oxidized by rabbit liver homogenates. Keto-evipal was formed, which is Evipal in which one of the methylene groups of the cyclohexenyl ring is oxidized to a carbonyl group. Therefore in the selection of a barbiturate the physician should avoid these short-acting types of drugs in individuals with hepatic disease.

van Dyke, Scudi, and Tabern (1947) prepared pentobarbital with a tagged nitrogen atom, namely $N^{15}$. They administered the compound orally to dogs and studied the excretion by following $N^{15}$. Dogs excreted about 60 per cent of the total dose of excess $N^{15}$ in the urine during the first 24 hours. The excess $N^{15}$ in the urinary ammonia and urea represented less than 8 per cent of the tagged atom. These workers concluded that more than 92 per cent of the dosage was excreted as metabolic products derived from the drug. Only 3 per cent of the total excess $N^{15}$ in the urine was found to be pentobarbital. It does appear from the investigations of Maynert and van Dyke (1949) and Brodie *et al.* (1953) that one of the major products of metabolism of pentobarbital is 5-ethyl-5-(3-hydroxy-1-methylbutyl) barbituric acid. Maynert (1952) observed that the principal metabolite excreted in the urine after administration of amobarbital was 5-ethyl-5-(3-hydroxyisoamyl) barbituric acid. The 2 metabolic pathways are similar and show that the oxidation in the liver occurs in the long side chain at position 5 by hydroxylation. The compounds with hydroxyl groups in the side chain are not hypnotics.

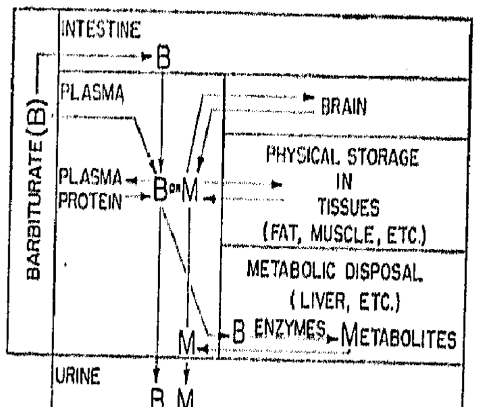


FIG. 26-2. A generalized, schematic diagram of the major pathways of the distribution and excretion of a barbiturate and its metabolites: B, barbiturate; M, metabolites. Arrows indicate direction of movement. (*Toman and Taylor, 1954.*)

Dorfman and Goldbaum (1947) studied the degradation of various barbiturates by tissue brei *in vitro*. Certain of their data are shown in table 26-2. Mark *et al.* (1958) showed that thiobarbiturates pass into the brain more rapidly than do their oxygen analogs. They attribute this to the greater degree of lipid solubility of the thiobarbiturates.

Evidence is convincing that the principal site of degradation of the short-acting barbiturates is the liver.

**Long- and short-acting barbiturates.** Fitch and Tatum (1932) were the first to recognize the distinct classification of barbiturates into long- and short-acting drugs. The classification has more recently been extended to include *intermediate* and *ultra-short*-acting barbiturates. Although these more definitive periods of activity are easily demonstrated in animals under controlled conditions, clinically, individual response and dosage level play such an important role that the original classification of Fitch and Tatum usually suffices.

Swanson and Fry (1940) showed the duration of action of various barbiturates by administering single oral anesthetic doses to dogs. The onset of action and the disappearance of symptoms were noted. These results are shown graphically by Swanson and Fry in figure 26-3.

**Toxic manifestations of barbiturates.** All individuals do not respond alike to the barbiturates. In some individuals the usual hypnotic dose is relatively ineffective. In others it may produce malaise, restiveness, excitement, delirium, and even hallucinations. In the management of hyperkinetic states in children, phenobarbital in some cases aggravates the condition and the administration of dextro amphetamine surprisingly confers tranquility upon the hyperkinetic child. As a rule however, the response is predictable. Dosage levels may vary for different individuals. Further, some appear to get better results with one barbiturate than with another.

TABLE 26-2

*Degradation of Barbiturates by Liver, Brain, and Muscle Brei*

(Dorfman and Goldbaum, 1947)

120 micrograms of appropriate barbiturate added to all vessels.

| Barbiturate | Liver Destruction | Brain Destruction | Muscle Destruction |
|---|---|---|---|
| | *per cent* | *per cent* | *per cent* |
| Secobarbital.......... | 30 | 0 | 0 |
| Thiopental........... | 53 | 10 | 0 |
| Phenobarbital........ | 0 | 0 | 0 |

Toxic manifestations resulting in death are practically unknown from therapeutic doses of barbiturates. Death from these drugs results from over-dosage.

In elderly individuals, especially where hepatic or renal disease is present, the barbiturate should be used with caution. Debilitated patients are more susceptible to the depressant action of these drugs. Besides, for short-acting barbiturates, hepatic metabolism is necessary for detoxification, and for long-acting barbiturates the kidney is depended upon for excretion. Skin rashes are rare following the administration of barbiturates.

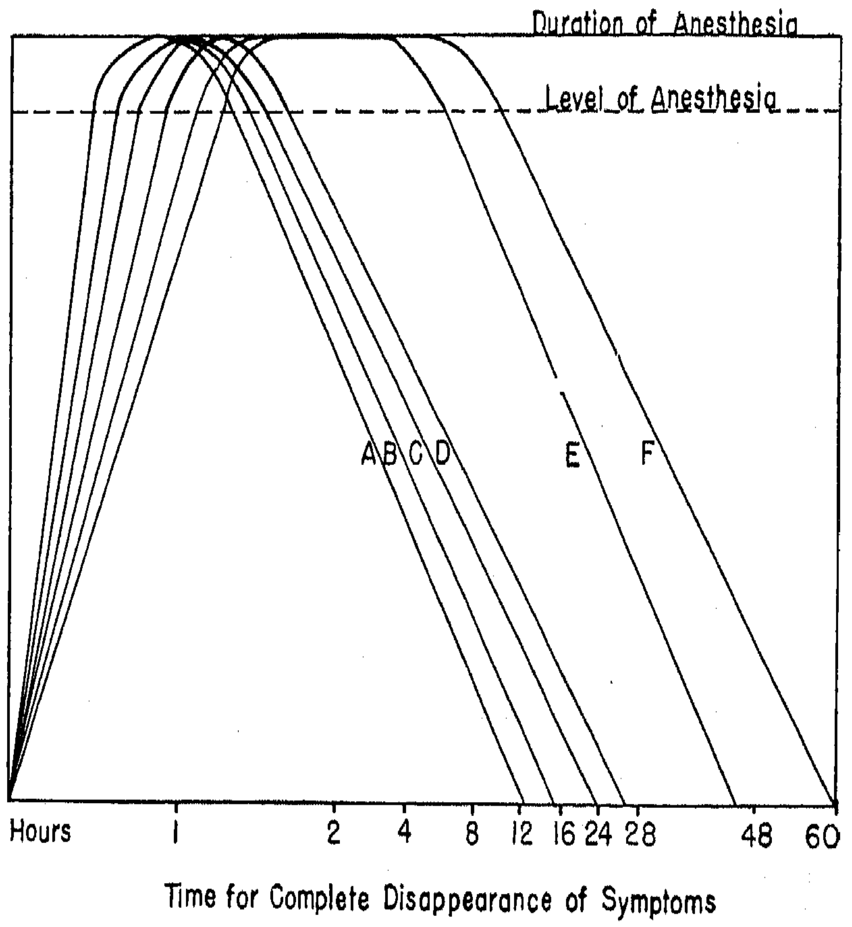


FIG. 26-3. Time of appearance, duration of anesthesia, and time needed for complete disappearance of symptoms after oral administration of equivalent single anesthetic doses in animals. A = Secobarbital sodium. B = Pentobarbital sodium. C = Amobarbital sodium. D = Amobarbital. E = Barbital sodium. F = Phenobarbital sodium. (*Swanson and Fry, 1940.*)

**Poisoning with barbiturates.** Barbiturates *kill by their central depressive action on the centers of respiration.* The respiration becomes shallow and slow. Nystagmus, strabismus, and diplopia are often present. The pupils are at first contracted but later dilated as hypoxia supervenes. Mental confusion and headache are frequently experienced. There may be a period of excitation before sleep. The syndrome may emulate that of alcoholic inebriety. Ataxia is usually manifested. As the respiratory depression continues the pulse becomes weak and rapid. The reflexes are sluggish and the skin clammy and cyanotic. The temperature drops as coma deepens.

Poisoning generally results from an over-dosage of the drug taken with suicidal intent. Or it may occur with an individual who is accustomed to taking the drug for hypnotic purposes. One dose is taken. He fails to go to sleep and forgets whether he has taken the drug or not. In this "twilight zone" of blurred consciousness he is likely to repeat the dose several times in an effort to get to sleep.

Severe poisoning usually occurs when the individual takes from 5 to 10 times the oral hypnotic dose. It is difficult to set definite toxic doses for the barbiturates. However, when 15 times the oral dose is taken the individual is likely to succumb despite restorative measures.

The prevalence of barbiturate poisoning is a matter of deep medical concern. In approximately 25 per cent of all cases in which persons are admitted to general hospitals owing to acute poisoning, barbiturates are the cause of the intoxication. Current insurance statistics point out that the barbiturates are the cause of death in 6 per cent of the suicides and 18 per cent of the accidental deaths of their policy holders (Hargrove *et al.*, 1952). The National Office of Vital Statistics of the United States Public Health Service reported that the number of deaths owing to barbiturate poisoning in this country increased from 266 in 1935 to 1143 in 1957. The New York City Poison Control Center reported 1111 cases of barbiturate intoxication in 1958.

**Treatment of barbiturate poisoning.** If the drug has been recently taken, induced emesis or gastric lavage is indicated to remove the portions of the dosage which have not passed from the stomach. Catharsis may also prove beneficial. The patient should be kept warm and if circulatory depression is present, 25 to 50 mg. ephedrine sulfate should be given subcutaneously. Dick (1952) used amphetamine sulfate in severe cases of barbiturate poisoning with success. He injected 40 mg. intravenously and followed this with 20 mg. every half hour. Levophed by intravenous infusion, page 549, may also be employed to elevate blood pressure. Other supportive measures were also included in the treatment.

The action of the drug is mainly on the respiratory mechanism. Hence, just as soon as measures have been taken to support the circulation and remove the drug, measures are then instituted to combat the respiratory depression. Oxygen inhalation is indicated. An endotracheal airway may be inserted to facilitate breathing. If required, artificial respiration by the back-pressure arm-lift method may be helpful.

Analeptic drug therapy in barbiturate poisoning appears to be of less importance than the foregoing procedures. If the patient responds to pain stimuli and deep tendon jerks are obtainable it is doubtful that the analeptic drugs are indicated. Generally the patient will work his way out of the narcosis with respect to time by metabolism and/or excretion of the barbiturate.

With patients who are more deeply narcotized, one of the following analeptics may be helpful. Each is believed to have facilitated the recovery of some patients in barbiturate intoxication and each has its strong advocates. The drugs are: (1) *caffeine and sodium benzoate*, (2) *nikethamide*, (3) *pentylenetetrazol*, (4) *methylphenidate hydrochloride*, (5) *Megimide*, and (6) *vanillic diethylamide*. Each drug is administered intravenously with its respective dosage schedule usually until the patient responds to painful stimuli. The dosage schedules of these analeptic drugs are found in chapter 31. It is our opinion that in the selection of an analeptic drug for this purpose the choices should begin with those agents which have proved to be the most benign. Therefore it would appear that caffeine and sodium benzoate or nikethamide should be selected if an analeptic is indicated.

Dobos *et al.* (1961) studied critically the value of analeptic drugs in 141 comatose patients with laboratory evidence of barbiturates in blood, urine or gastric washings. Of the group, 77 received analeptic therapy and 64 were treated supportively without analeptics. There were 4 deaths in the first group and 2 in the second. The major complication of the coma was bronchopneumonia; this contributed to 3 of the total of 6 deaths. They conclude, "Meticulous supportive care is, at present, the therapy of choice in acute barbiturate intoxication." This view was expressed previously by Hayes (1958).

Other measures of importance in barbiturate poisoning are the administration of adequate penicillin therapy to protect against pneumonia and the intravenous infusion of plasma or 5 per cent glucose in saline. This latter step protects the patient against secondary shock and provides for the maintenance of adequate water balance.

**Hemodialysis in barbiturate poisoning.** Hemodialysis by means of the "artificial kidney" has been used successfully in the treatment of barbiturate poisoning (Kyle *et al.*, 1953). From investigations on the relative efficacy of the procedure for the removal of the barbiturates from blood, it was observed that the hemodialysis is 20 to 30 times more effective than the urinary excretion of barbiturates. Kyle states, "Patients with barbiturate poisoning tolerate the hemodialysis well and show an improvement in clinical status during the dialysis." Dobos *et al.* (1961) state that, "In the unusual instance of prolonged coma due to the ingestion of large amounts of barbiturates, hemodialysis may be a life-saving measure." Exchange transfusion is valuable if the facilities for hemodialysis are not available.

**Habituation and tolerance with barbiturates.** Laboratory animals can be shown to develop tolerance to barbiturates. Gruber and Keyser (1946) found dogs to become tolerant to a variety of barbiturates. They used as a criterion of tolerance a reduction of the sleeping time elicited by the same dose after it had been repeated several times. The tolerance appeared to be a cross-tolerance for all the barbiturates studied. The tolerance was soon lost by withdrawal of the drug. It is of interest that the developing of tolerance as shown by a decrease in the sleeping time offered no protection from death when the $LD_{50}$ dose was administered.

This tolerance is manifested in man to a limited extent. Butler *et al.* (1954) demonstrated that tolerance to the hypnotic effect of phenobarbital in man somewhat exceeds the accumulation of the drug in the plasma and masks any clinical evidence of accumulation. It appears to be motivated by a strong psychogenic factor which may cause the habitué to take larger doses and more frequent doses of the drug. There is usually produced, however, no physical dependence on the drugs. There is no syndrome of withdrawal symptoms as occurs in the morphine addict upon abstinence from a small dosage schedule. Therefore it appears more accurate to refer to the phenomenon as habituation rather than true addiction. This view is shared by Tatum (1939) and others who have studied the problem. However, when large doses of barbiturates are administered repeatedly for long periods of time, and then withdrawn, an abstinence syndrome occurs which resembles *grand mal* convulsions. The investigators at the U. S. Public Health Service Hospital in Lexington, Kentucky, have shown that continued large doses of barbiturates may produce physical dependence as well as habituation and tolerance. The addict appears not to be satisfied with doses of the barbiturate that do not produce severe intoxication (1.5 to 2.5 gm. daily.) The subjects are euphoric, but also confused and ataxic. They are frequently obstinate and abusive. This is in marked contrast to the morphine addict who remains passive and often well oriented to environmental situations (Wikler, 1952).

Fraser *et al.* (1958) studied the degrees of physical dependence evoked by secobarbital and pentobarbital when administered at high dosage levels to volunteers and abruptly withdrawn. The duration of medication was from 32 to 365 days. Convulsions and delirium occurred upon withdrawal of high dosage levels in most cases. They found a daily dose greater than 400 mg. necessary to elicit physical dependence.

**The therapeutic uses of the barbiturates.**

1. The principal use of the barbiturates is to produce *sedation* and *sleep*. They allay anguish, apprehension, and tenseness. They restore tranquility, relaxation, and composure. The sedation is valuable in hypertension, menopausal symptoms, hyperthyroidism, paralysis agitans, dysmenorrhea, chorea, hysteria, allergic disorders, peptic ulcer, and motion sickness. For general sedation, phenobarbital is the drug of choice. Evidence is not convincing that the more expensive tranquilizing drugs with their larger dosage schedules are superior to phenobarbital in allaying the emotional trauma of many organic diseases.
2. *Use in insomnia.* The barbiturates are most useful in insomnia resulting from fear, apprehension, solicitude, or anguish. When sleep is induced by a rapidly acting barbiturate such as secobarbital sodium, the patient generally sleeps through the night. The effect comes on in 15 to 20 minutes and disappears in 3 to 4 hours. Therefore upon arising the patient is seldom drowsy from the drug effect in the morning. If the patient gets to sleep easily but awakens in 4 to 5 hours, the drug is given in an "Enseal" which dissolves very slowly. Its effect begins in a period of 4 to 5 hours.

   Longer acting barbiturates such as amobarbital and phenobarbital may also be employed. A mixture of equal parts of secobarbital sodium and amobarbital sodium, known as "Tuinal" is useful for short and intermediate hypnotic action.

   In insomnia caused by cough, codeine may be given along with a barbiturate.

   When insomnia is caused by pain it is not wise to increase the barbiturate dosage in an effort to attain analgesia. It is better practice to use an analgesic such as acetylsalicylic acid in conjunction with a normal hypnotic dose of a barbiturate.

   Repetitious use of the barbiturates nightly may lead to habituation. The physician should endeavor to remove the sleep-inducing drug just as soon as the emergency for which it was prescribed has passed.
3. *Anticonvulsant uses.* The barbiturates depress hyperexcitability of the motor cortex. Phenobarbital is the most striking of the barbiturates for this purpose. Phenobarbital is one of the most important drugs used in the treatment of epilepsy. Its use in this condition is discussed more fully under the special heading of *Epilepsy*, page 425.

   Other convulsive seizures in which the barbiturates are found useful are tetanus, strychnine poisoning, and chorea. The barbiturates are used to combat the convulsive seizures produced by local anesthetics.

   The thiobarbiturates and methohexital are used to suppress the convulsions of electric shock therapy in mentally ill patients.
4. *Preanesthetic medication.* The use of the barbiturates for this purpose is discussed on page 311.
5. *Anesthesia with the barbiturates.* This has been discussed in page 333.
6. *Barbiturates in obstetrics.* The barbiturates have been used extensively to produce obstetrical amnesia. Although they have their limitations in this field, they serve to make the experience less disagreeable to the mother and are believed not to harm the infant. Secobarbital, pentobarbital, and amobarbital have been employed for this purpose. They do not prolong the dilatation of the cervix or interfere with the strength of uterine contraction. A dosage schedule for the 3 drugs in obstetrics is given in table 26-3.

TABLE 26-3

*Dosage Schedule for Barbiturates in Obstetrics*

| | Secobarbital Sodium | Amobarbital Sodium | Pentobarbital Sodium |
|---|---|---|---|
| Initial dose when labor is definitely established | 0.2 to 0.3 gm. | 0.2 to 0.4 gm. | 0.1 to 0.2 gm. |
| Subsequent doses at 1 to 3 hr. intervals | 0.03 to 0.2 gm. | 0.2 to 0.4 gm. | 0.1 to 0.2 gm. |
| Total dose | 0.8 gm. | 1 gm. | 0.5 gm. |

7. *Barbiturates in pediatrics.* The drugs have been used successfully in pediatrics to sedate unruly children for many different routine procedures such as examinations of the nose, throat, and ears.
8. *Barbiturates in neuropsychiatry.* The barbiturates are used for prompt and prolonged hypnosis for psychologic study. Amobarbital sodium appears to be the drug of choice.

   The restoration of restful sleep in acute excitement is another function of the barbiturates.

   Amobarbital sodium sedation has been used to establish the prognosis for schizophrenic patients. The more normal the patient's behavior pattern under the influence of the drug the more hopeful the prognosis.

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# 27

# *Central Nervous System Depressants. Hyperkinesia: Epilepsy, Paralysis Agitans, and Chorea*

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The treatment of epilepsy until 1938 was confined mainly to the use of two drugs. These were the bromides and phenobarbital. Each of these substances presented the disadvantage in therapy of depressing the sensory cortex as well as the motor cortex. It was therefore deemed desirable to obtain a drug which mainly affected the motor areas. The advantage of such a compound is obvious. It would control the epileptic seizure without interference with the mental alacrity of the individual.

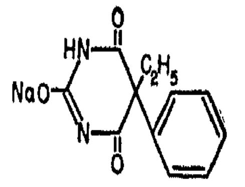
Arthur Dox of the Parke, Davis Research Laboratories, who was one of the American pioneers in barbituric acid derivative synthesis, had prepared such a compound many years ago. However, the aim of his synthetic procedures was to obtain a more efficient and less toxic barbiturate or related compound. Therefore the screening procedures which were employed to examine his products were designed only to evaluate them as hypnotics. Therefore *Diphenylhydantoin Sodium, U.S.P.* (*Dilantin*) was discarded as a drug of no value.

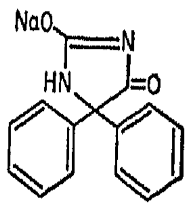
## DIPHENYLHYDANTOIN SODIUM

In 1938 Merritt and Putnam investigated a series of anticonvulsant compounds. They measured the capacity of these substances to increase the threshold of the motor cortex of cats to electrical stimulation. Because of the similarity in structure of diphenylhydantoin to the barbiturates, it was supplied to these investigators by Oliver Kamm of the Parke, Davis Research Laboratories, where it had occupied a position on the shelf for years. Merritt and Putnam found diphenylhydantoin to offer excellent protection against the convulsive seizures of electrical stimulation in the cat. What is more, the compound did not evoke hypnosis. The advantage of such a substance in the treatment of epilepsy became manifest to these workers. The correctness of their judgment is attested by the fact that diphenylhydantoin has enjoyed a quarter-century of use in the successful management of epilepsy.

The relationship of diphenylhydantoin to phenobarbital is shown in the following formulas. It will be observed that hydantoin is a glycolylurea. It will be recalled that barbituric acid is malonylurea.

**Pharmacologic response to diphenylhydantoin.** The principal pharmacologic response to diphenylhydantoin is a depression of the motor cortex. The drug accomplishes this without appreciable effect upon the sensory areas. Gruber *et al.* (1940) demonstrated that the drug showed a wide margin of safety. When it produces death in laboratory animals, the death results from respiratory paralysis.


Phenobarbital Sodium Salt
(Phenylethyl Barbituric
Acid Sodium)


Dilantin Sodium Salt
(Diphenylhydantoin
Sodium)

Goodman and Lih (1941) showed that when diphenylhydantoin is administered repeatedly several days in advance, it will decrease the incidence of convulsions in laboratory animals produced by pentylenetetrazol. The spinal convulsions of strychnine and the convulsions originating in the midbrain from cocaine are not effectively antagonized by diphenylhydantoin.

**Mechanism of action.** Diphenylhydantoin does not markedly affect the seizure threshold but prevents the degree of spread of the epileptic discharge throughout the brain (Toman *et al.*, 1946). Thus the abolition of the tonic phase of the maximal seizure following diphenylhydantoin therapy is believed to be due to decreased involvement of other brain areas.

An important contribution to our knowledge regarding the mechanism of the action of diphenylhydantoin was made by Woodbury (1956). Diphenylhydantoin was shown to elevate the electroshock threshold (EST) in rats by 17 per cent. The drug decreased the total and intracellular concentration of sodium in the brain. The ratio of extracellular to intracellular brain sodium was increased. Intracellular brain sodium was increased by electroshock seizures in the animals. Brain potassium was not significantly affected. Woodbury interpreted his findings to indicate that the anticonvulsive activity of diphenylhydantoin was associated with the capacity of this drug to extrude intracellular brain sodium and thus suppress the convulsion-activating process.

Esplin (1959) studied the effect of diphenylhydantoin, using the anticonvulsive in nontoxic doses, on the various aspects of synaptic transmission in the spinal cord and stellate ganglion of unanesthetized cats. Stimuli were applied either to a peripheral nerve or to dorsal root ($L_7$ or $S_1$). Maximal isolated monosynaptic responses were reduced about 10 per cent and polysynaptic potentials were reduced about 30 per cent. Diphenylhydantoin did not affect either direct facilitation or inhibition of the spinal cord. The drug enhanced transmission failure during repetitive stimulation. The response deficit evoked by diphenylhydantoin was pronounced in the ganglion but was only slightly manifested in the monosynaptic and polysynaptic pathways of the spinal cord. Diphenylhydantoin elicited a marked reduction in post-tetanic potentiation, which was attributable to a specific suppression of the potentiation process. The investigator suggests that since post-tetanic potentiation, including enhancement of transmission during tetanic stimulation, is involved in the spread of seizure discharge, the reduction of post-tetanic potentiation by diphenylhydantoin is a facet of its anticonvulsive action.

Blum (1961) showed that carefully regulated intravenous doses of diphenylhydantoin depressed the electrical response in the pyramidal tract resulting from stimulation of the motor cortex. These doses had an insignificantly small effect on the postcruciate sensorimotor pyramidal response to stimulation. Larger doses indiscriminately affected the motor and sensorimotor response. This investigator proposes that the selectivity in depression of response to the motor cortex may be related to the fact that the drug is anticonvulsive and nonhypnotic.

**Absorption, fate, and excretion.** The sodium salt of diphenylhydantoin is very alkaline in aqueous solution, pH 11.7. It is not available by vein. When given by mouth the compound is readily absorbed from the gastrointestinal tract. Under therapeutic dosage in the treatment of epilepsy, the blood concentrations of the compound lie between 3 and 6 mg. per cent (Kozelka and Hine, 1940).

Firemark *et al.* (1963) used $C^{14}$-labeled diphenylhydantoin to study the brain distribution of the drug in cats. Penetration of the brain was rapid, and the levels paralleled the vascularity of the brain. The accumulation of diphenylhydantoin per dry weight of brain solid was found to be higher in the gray matter than in the white matter, suggesting that the binding of the drug in the brain is probably to nonlipid constituents.

Only a small fraction of the dose of diphenylhydantoin is excreted in the urine unchanged (1.2 per cent). Kozelka and Hine (1943) also found hydantoic acid and α-aminodiphenyl acetic acid in the urine of human subjects ingesting diphenylhydantoin. The quantities of these products excreted represented less than 5 per cent of the dose of diphenylhydantoin, indicating that the compound undergoes marked degradation in the body.

Using 4-$C^{14}$-labeled diphenylhydantoin, Noach *et al.* (1958) studied the absorption, distribution, fate, and excretion of the compound. Chemical alteration of the molecule occurs principally in the liver. The major route of excretion of diphenylhydantoin is into the gastrointestinal tract, from which absorption takes place. Metabolites in the gastrointestinal tract result from biliary excretion. Excretion was also found to occur in the saliva.

**Untoward effects.** The principal untoward reactions to diphenylhydantoin are dizziness, muscular incoordination, gastric distress, swelling of the gingivae, and weight loss (Lennox, 1942). Of these, muscular incoordination is the most frequent. None of these symptoms is severe, and they serve as a warning to the alert physician to diminish the dose temporarily or discontinue the drug for a short period. When gastric disturbance persists, the oil suspension of the drug in capsules may be less irritating to the gastrointestinal tract than the capsules of the dry alkaline sodium salt of diphenylhydantoin. Other symptoms that have been reported are skin rash, tremors, nystagmus, and mental confusion.

The severe gingival hyperplasia which has been noted in rare cases following the administration of diphenylhydantoin was once believed to be the result of altered ascorbic acid metabolism caused by the drug (Drake *et al.*, 1941). Emmett *et al.* (1943) showed that the utilization of ascorbic acid was not affected by the administration of diphenylhydantoin.

Moore (1959) described a series of patients in which pulmonary changes were found to be definitely related to anticonvulsives containing the hydantoin nucleus, including diphenylhydantoin and Mesantoin. Diffuse fibrosis was found by roentgenographic examination of the lungs in 16 of 31 patients who had been on hydantoin therapy for 2 years or more. Of special interest is the fact that 6 of 15 patients with normal lungs had gingival hyperplasia, as compared to no hyperplasia in the 16 patients with abnormal lungs. Since the gingival hyperplasia is considered to be an allergic response to hydantoin, Moore considers that this effect may be manifested in tissues other than the gingivae.

Francis and Melville (1959) observed that human gingivae contain very low concentrations of histamine, but the tissue is rich in serotonin. Inflamed gingival tissue was shown to contain a high histamine level, but no serotonin. Hyperplastic gingival tissue from a patient treated with diphenylhydantoin contained a low histamine level and a complete absence of serotonin.

Shapiro (1958) used diphenylhydantoin to accelerate wound healing of the gingivae in nonepileptic patients. In 33 of 52 patients receiving the drug there was observed uneventful healing of gingival wounds, with marked fibroblastic activity, clot organization, and epithelial proliferation. The action was attributed to the action of diphenylhydantoin or one of its metabolites upon the plasma cells. This is an interesting therapeutic application of what is considered one of the adverse side effects of diphenylhydantoin.

Rosenfeld *et al.* (1961) reported a case of a syndrome simulating lymphosarcoma from diphenylhydantoin therapy in a patient. The signs and symptoms disappeared upon drug withdrawal, and a recrudescence occurred upon reestablishing therapy. They are of the opinion that the syndrome is associated with sensitivity to drugs of the hydantoin type.

Tolerance to diphenylhydantoin does not appear to develop. The initial dose found effective in controlling convulsions may be maintained as a rule. Increased dosage is generally not necessary.

**Parenteral diphenylhydantoin.** Murphy and Schwab (1956) developed a solution of diphenylhydantoin sodium suitable for parenteral injection. The solution contains 5 gm. of diphenylhydantoin sodium, 10 ml. of ethanol, 40 ml. of propylene glycol, and water sufficient to make 100 ml. They have used this solution successfully in the treatment of *status epilepticus* and for the prophylactic control of seizures in neurosurgery. The solution was used intramuscularly without reactions at the site of injection or tenderness, in quantities containing as much as 1 gm. of the drug. In *status epilepticus* they employed 150 to 250 mg. intravenously. The advantage of diphenylhydantoin over phenobarbital in these procedures is the avoidance of the severe respiratory depression caused by the latter drug.

**Therapeutic uses.** The principal use of diphenylhydantoin is in the *treatment of epilepsy.* The average dose is 0.3 to 0.9 gm. daily. Its use in this disease is discussed on page 414. It has been used with limited success in the control of Sydenham's chorea, Parkinson's syndrome, migraine, and delirium tremens. Lamberts (1959) used diphenylhydantoin in the treatment of trigeminal neuralgia with success in 30 patients of various age groups; the dosage schedule was 100 mg. 3 times daily. In certain cases the intractable pain of the tic douloureux returned, and more heroic measures were necessary. His best results were achieved in the older age group of patients.

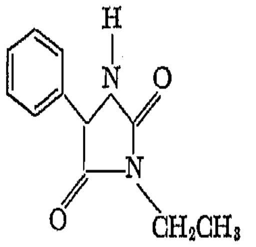
### OTHER HYDANTOIN ANTICONVULSIVES

**N-methylphenylethyl Hydantoin Sodium (Mesantoin)** is used as an anticonvulsive. It is claimed that the gingival hyperplasia has never resulted from its administration. Tolerance, however, develops with the use of the drug. Neurological disturbances such as *ataxia, tremor, vertigo, diplopia,* and *nystagmus* do not occur with Mesantoin therapy. Skin rash, however, has resulted from the use of the drug but generally disappears after its discontinuance for a few days.

Loscalzo (1947) used Mesantoin in 67 cases of epilepsy over a period of 3 years. *Grand mal seizures* were reduced about 60 per cent with an accompanying improved emotional status. *Petit mal* and *psychomotor* types of epilepsy were not improved by Mesantoin. The drug did not appear to be toxic. One to 6 tablets of Mesantoin 0.4 gm. were given daily. The average dose is 4 tablets daily. Butler (1952) studied the metabolic fate of Mesantoin in the dog and man. The compound is demethylated by each species and excreted in the urine as 5-ethyl-5-phenyl hydantoin (Nirvanol). It is of interest that Nirvanol has not been used in recent years in the treatment of epilepsy, owing to its toxicity. Now it becomes apparent that Mesantoin is converted into Nirvanol by the body. If Mesantoin is sufficiently nontoxic for use in epilepsy and is also clinically effective, the rejection of Nirvanol seems unjustified (Butler, 1952).

Weller and Metcalfe (1949) reported a case of fatal *pancytopenia* from the use of Mesantoin. Hunter and Jenkins (1951) reported 6 cases of skin pigmentation during Mesantoin therapy. Biopsy showed the pigment to be melanin. The pigment disappeared when therapy was discontinued. Clinical studies failed to disclose any basic functional disturbance of the adrenal glands.

**Ethotoin (Peganone).** Peganone is another hydantoin derivative that is used in the treatment of the grand mal type of epilepsy. Its structure is shown in the formula:



Ethotoin
Peganone
(3-ethyl-5-phenylhydantoin)

Peganone is a white, crystalline powder which is sparingly soluble in water.

Schwade *et al.* (1956) studied the pharmacology of Peganone. As an anticonvulsive, it was more effective against electroshock seizures than against the convulsions evoked by pentylenetetrazol. Long-term feeding experiments indicated no damage to the viscera or alterations of the blood picture of laboratory animals. Experiments indicated that Peganone is degraded in the liver.

As an anticonvulsive Peganone requires a larger dose than many similar drugs; however, its toxicity also appears to be less than that of many of the drugs currently used in the treatment of epilepsy. Like diphenylhydantoin it does not produce drowsiness and in this respect differs from phenobarbital and mephobarbital. Schwade *et al.* (1956) reported on the use of Peganone over a 2-year period in the treatment of over 1000 epileptics. There were no cases of renal impairment or hepatotoxic action attributable to the drug. Of special interest is the fact that no blood dyscrasias were encountered. Peganone is reported to be effective when used alone in satisfactorily controlling seizures in 58 per cent of 500 patients with grand mal epilepsy. In the other variants of epilepsy it is less effective.

Livingston (1956) compared Peganone to diphenylhydantoin in the treatment of grand mal epilepsy. He was able to control completely 9 of 27 cases with Peganone alone. The average daily dose was 3 gm. There were fewer side effects with Peganone than with diphenylhydantoin; gum hyperplasia and ataxia were not encountered with Peganone.

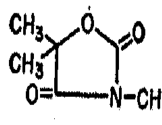
Other clinical reports on Peganone confirm those cited. It does appear that Peganone is another welcome addition to our increasing number of anticonvulsives and is useful in controlling a segment of patients with grand mal epilepsy. In conjunction with other drugs its effectiveness is definitely increased. Its salient feature appears to be the comparative absence of side effects. Side effects that have been reported are *dizziness, headache, fatigue, skin rash, diplopia, nystagmus, diarrhea, insomnia, fever,* and a *sensation of numbness.* However, these are not frequently encountered and are sufficiently mild that they can be controlled by reduction of dosage.

Peganone is supplied in tablets of 250 and 500 mg. The average adult dose is 2 to 3 gm. daily. Dosage schedules in adults below 2 gm. daily are usually ineffective.

### TRIMETHADIONE

Everett and Richards (1944), in seeking compounds that would serve as analgesics, found the compound having the structure 3,5,5,-trimethyloxazolidine-2,4-dione to be approximately as efficient as aspirin. It also elicited some sedative action. This prompted its trial in epilepsy. It was found of little value in the treatment of *grand mal* but especially useful in the control of the seizures of *petit mal.*

Structurally the compound may be related to diphenylhydantoin, as shown (see formula). Removing one of the amino groups from the hydantoin nucleus and substituting an oxygen atom in the ring, we have, after appropriate methylation, the structure of trimethadione.



Trimethadione, U.S.P.
Tridione

Trimethadione is a white, crystalline powder with a faint balsamic odor. Soluble to about 5 per cent in water, it forms neutral solutions. Its solubility is greatly enhanced by urethane and alcohol. Trimethadione is administered orally. It is usually given in capsules containing 0.3 gm.

Everett and Richards (1944) found trimethadione effective in antagonizing convulsions induced in mice, guinea pigs, cats, and rabbits by the administration of various convulsant drugs, including pentylenetetrazol, strychnine, picrotoxin, thujone, cocaine, and procaine. Trimethadione also increases the threshold at which electrically-induced convulsions can be produced. As the result of pharmacologic studies showing its anticonvulsive properties, trimethadione was studied clinically in the treatment of epilepsy.

**Absorption and excretion.** In laboratory animals and in human subjects, trimethadione is readily absorbed from the gastrointestinal tract. Therapeutic doses produce slight sedation and analgesia. Larger doses produce ataxia. Doses in the order of magnitude of 2 gm./kg. elicit sleep, unconsciousness, and respiratory depression.

Trimethadione injected intravenously into dogs (50 mg./kg.) produces a transient depressor response. The response is diminished by reducing the speed of injection.

The toxicity of trimethadione as measured in laboratory animals is low (Everett and Richards, 1944). No significant changes were produced in the vital organs or blood picture of animals after prolonged administration of the drug in doses of from ⅙ to ¼ of the $LD_{50}$.

Richards *et al.* (1946) observed that liver damage or bilateral nephrectomy prolonged the hypnotic action of trimethadione in laboratory animals. It appears, therefore, that the substance is probably detoxified in the liver and excreted by the kidneys. In man, however, only 3 per cent of a single large therapeutic dose can be detected chemically in the urine. The compound appears to undergo degradation in the human body.

The metabolic fate of trimethadione in the dog was studied by Butler *et al.* (1952b). Partial demethylation occurs since 5,5-dimethyl-2,4-oxazolidine-2,4-dione appears in the urine; this compound is slowly excreted.

**Untoward effects.** The most persistent untoward action of trimethadione is that of producing a visual disturbance referred to as a "glare phenomenon," "hemeralopia," or a distinctive type of photophobia. The individuals when outdoors see bright objects as though they were covered with snow. They shun the light and resort to wearing dark glasses. The effect is reversible. It appears in susceptible persons about a week after trimethadione therapy is begun and disappears a few days after the drug is withdrawn. Dekking (1950) found that the vivid sensations of glare and almost total disappearance of color in brightly lighted objects which sometimes follows use of trimethadione are caused by a specific action on the retinal cones. It interferes with their light adaptation. Dark adaptation is not influenced by this drug. It is the opinion of workers in this field that if the effect persists and causes much distress, the drug should be withdrawn, at least until the mechanism of this action is more clearly understood.

Nausea is produced by the drug in occasional cases. This generally disappears if the drug is withdrawn and dosage is reinstituted later at a lower level. The dosage may then be increased to therapeutic levels without the recurrence of the gastrointestinal distress.

Skin rash is rare. Should it occur, the same type of withdrawal and reestablishment of dosage as was recommended in the foregoing paragraph under gastrointestinal distress will often obviate the difficulty.

Harrison *et al.* (1946) encountered a fatal case of aplastic anemia after the administration of trimethadione and a hydantoin. Mackay and Gottstein (1946) reported a case of fatal agranulocytosis in a 23-year-old woman to whom trimethadione was administered in the treatment of petit mal epilepsy. Other cases have been reported. This should alert the physician to the necessity of blood studies on patients receiving the drug. Temporary depression of the leukocyte count may occur in some adult patients but seldom in children. If the leukocyte depression persists, the drug should be discontinued. It is good practice to check monthly the blood picture of patients taking trimethadione.

TABLE 27-1

*Tridione in Convulsive Seizures*

(Richards and Everett, 1946)

| Drug | Protective Dose Against Pentylenetetrazol | Clinical Evaluation | |
|---|---|---|---|
| | | Grand mal | Petit mal |
| | *mg./kg.* | | |
| Oxazolidine-2,4-dione | | | |
| 3,5-dimethyl | 500 | ? | ++ |
| 3,5,5-trimethyl (trimethadione) | 500 | + | +++ |
| 3,5-dimethyl-5-ethyl (paradione) | 250 | ? | ++ |
| Barbituric acid | | | |
| 1,5,5-trimethyl | 100 | + | – |
| 5,5-diethyl-1-methyl | 50 | ++ | – |
| Phenobarbital | 50 | +++ | – |

**Therapeutic uses.** The principal therapeutic use of trimethadione is in the treatment of the *petit mal type of epilepsy*. The specificity of the drug for this condition is shown by the data of Everett and Richards (1946) (table 27-1). In this table certain of the oxazolidine 2,4-dione derivatives are compared with barbituric acid derivatives in protecting animals from pentylenetetrazol convulsions. These data are compared with the efficacy of the compounds in controlling petit mal and grand mal types of epilepsy.

From these results it may be concluded that the anticonvulsant action of these drugs against pentylenetetrazol gives a useful index of antiepileptic activity. It does not, however, differentiate between the drugs effective in grand mal or petit mal.

A further discussion of trimethadione appears later in this chapter in the section on the comparative value of anticonvulsive drugs in epilepsy.

**Paradione.** The compound listed in table 27-1 as 3,5-dimethyl-5-ethyloxazolidine-2,4-dione, is available under the name of *Paradione, Paramethadione.* It is trimethadione in which one of the methyl groups on C-atom 5 has been extended to an ethyl group. The compound is an oily liquid which is slightly soluble in water but readily soluble in alcohol.

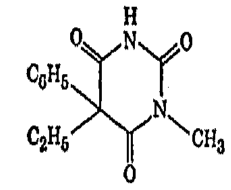
The use of Paradione in therapy is identical with that of trimethadione. It appears that in cases where trimethadione is ineffective, Paradione may be useful. Conversely, in cases where Paradione gives disappointing results, trimethadione may be found effective.

The doses of Paradione and trimethadione are approximately the same, namely, 0.3 gm., with a daily dosage schedule of 0.9 to 1.8 gm. Paradione is reported to produce a lower incidence of visual disturbance than trimethadione. Other minor untoward actions of trimethadione have been reported to be less severe with Paradione. With Paradione therapy neutropenia has been reported.

### Motor Depressant Barbiturates

**Phenobarbital Sodium, U.S.P.** The description and general use of this important barbiturate is discussed on page 400. Its use in the treatment of epilepsy is developed on page 425.

**Mephobarbital, N. F. (Mebaral).** Mephobarbital is a barbiturate used mainly for its depressant action on the motor areas of the brain. Chemically it is N-methylphenobarbital, as shown in the formula below.



Mephobarbital, N.F.
Mebaral

Mephobarbital exerts a sedative action similar to that of other barbiturates. Its action as a hypnotic is very mild. In common with phenobarbital, mephobarbital produces a strong anticonvulsive action on the motor cortex. Mephobarbital, therefore, finds its special field of usefulness in the treatment of epilepsy.

Butler *et al.* (1952a) showed that in dogs and man mephobarbital is demethylated and hence converted into phenobarbital. The site of demethylation appears to be the liver. Chronic oral administration leads to the accumulation of phenobarbital but not of mephobarbital. In man, when mephobarbital is given orally, plasma concentrations of phenobarbital are higher than those of mephobarbital. Besides, the compound appears to be poorly absorbed from the intestine of the dog. This study indeed poses the question of the value of this drug as an anticonvulsive. Phenobarbital is safer and more dependable.

Furthermore, Gluckman and Gruber (1952) showed that mephobarbital produces tolerance in rabbits. This tolerance to mephobarbital is also a cross-tolerance to butabarbital sodium, which is a typical dialkylbarbiturate.

Mephobarbital is used mainly in the treatment of grand mal epilepsy. The daily dose of the compound is from 0.2 to 0.8 gm. in tablets. Mephobarbital is claimed to offer an advantage over phenobarbital in that it produces less drowsiness. As mephobarbital appears to be converted into phenobarbital in the body, it is doubtful whether this claim can be substantiated.

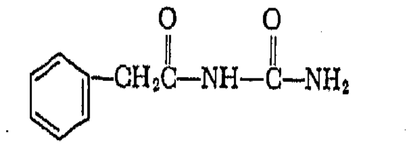
**Metharbital (Gemonil).** Gemonil is an anticonvulsive barbiturate similar in its action to phenobarbital and mephobarbital and used in the treatment of grand mal epilepsy. It is 5,5-diethyl-1-methyl-barbituric acid. This barbituric acid derivative is less toxic to mice when administered acutely than is phenobarbital. It is reported also to produce less drowsiness than phenobarbital. Other side effects of therapy with Gemonil are *skin rash, dizziness,* and *gastrointestinal distress.*

In addition to the use of Gemonil in the treatment of grand mal epilepsy, the drug has been found useful in the treatment of monoclonic spasm of infancy and related disorders. There appears to be no crucial evidence to indicate that Gemonil is superior to phenobarbital in the control of grand mal epilepsy.

Gemonil is available in 100-mg. tablets. The daily dose initially is 300 mg. and may be increased to 600 or 800 mg. if the lower dosage schedule is not effective in controlling seizures.

### Other Anticonvulsives

**Phenacetamide (Phenurone).** Another type of anticonvulsive is Phenurone; its structure is shown in the formula below.



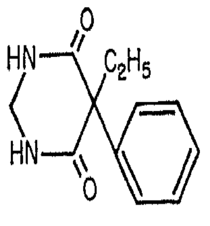
Phenylacetylurea
Phenurone

Phenurone occurs as a white or creamy white, crystalline powder. It is tasteless and odorless, and sparingly soluble in water. This compound has been found to combat electric shock convulsions in various laboratory animals, and therefore it was employed clinically in the treatment of epilepsy.

Phenurone is recommended in psychomotor epilepsy, grand mal, and mixed seizures. The drug appears to be of little value in petit mal and myoclonic-type seizures. The use of the drug is frequently connected with many serious side effects, and it should be employed only after failure with other anticonvulsives. Among the difficulties encountered are *personality changes* including *toxic psychoses, hepatic damage,* and *aplastic anemia. Gastrointestinal distress, general malaise, fever,* and *anorexia* have also followed the administration of Phenurone. It appears that the use of this anticonvulsive entails a considerable risk, and it should be employed only after these hazards have been weighed against the possible benefits to the patient. The cogency of this statement is emphasized by the use of Phenurone in a series of patients reviewed by Craddock (1955). Hepatic coma was reported as the terminal feature of 6 patients who died under treatment with Phenurone. *Disordered mental state, fever, fetor hepaticus, Kussmaul-type respiration, dryness of mucous membranes, muscular twitching,* and *oliguria* were among the findings which preceded death.

The dose of Phenurone is based upon the patient's response. The initial dose is 0.5 gm. 3 times a day with meals. If no untoward effects are encountered, the dosage schedule may be gradually increased to 2 or 3 gm. per day.

**Primidone, U.S.P. (Mysoline)** is a pyrimidine derivative. It is phenobarbital in which the urea oxygen atom has been replaced by 2 hydrogen atoms as shown in the following formula:



Mysoline, U.S.P. (Primidone)
(5-phenyl-5-ethyl-hexahydropyrimidine, 4, 6-dione)

Primidone occurs as a white, crystalline powder; it is tasteless and insoluble in water.

*Pharmacologic action.* The anticonvulsive action of primidone in laboratory animals was demonstrated by Bogue and Carrington (1953). Goodman *et al.* (1953) confirmed these studies using electrically-induced seizures in mice and rats. The acute toxicity of primidone in rats was found to be between 1.5 and 2 gm./kg.; the protective dose against electrically-induced seizures was 5 mg./kg. Thus the margin of safety of primidone is high.

Primidone is well absorbed from the gastrointestinal tract, yielding the maximal blood levels in about 1 hour after ingestion. The maximal effect of the drug is achieved in between 6 and 8 hours after a single dose. From 60 to 80 per cent of primidone is excreted in the urine during 24 hours. Approximately ½ of the therapeutic dose is excreted unchanged and the remainder as phenylethylmalon-diamide.

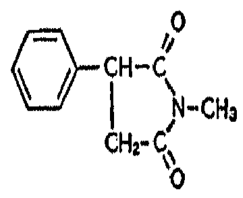
**Therapeutic use.** Primidone has had clinical trial in the treatment of epilepsy in several clinics. Handley and Stewart (1952) and Doyle and Livingston (1953) are of the opinion that primidone will effectively control major motor epilepsy. It was found, however, to be ineffective in the control of *petit mal, minor motor,* and *psychomotor seizures.* Primidone is often given along with the other anticonvulsive drugs such as mephobarbital and Mesantoin. Timberlake *et al.* (1955) observed primidone to be an effective anticonvulsant in 54 per cent of a series of patients with the different variants of epilepsy. Their data show the best results against the *grand mal seizures.*

Livingston and Petersen (1956) used primidone in 192 patients who had never received any other therapy for their seizures. They found primidone to be effective only in the control of grand mal seizures, in contrast to certain others who have reported its value in petit mal and psychomotor attacks. Side effects occurred in about half of the patients.

The side reactions of primidone that have been reported are *drowsiness, ataxia, vertigo, irritability, general malaise, nausea, vomiting,* and *occasional skin rash.* These side effects are generally mild and can be obliterated by reduction of dosage. The initial dose in some cases precipitated side reactions which subsided as treatment was continued. Other side effects of a more serious nature from primidone therapy have been reported. For example, Newman and Sumner (1957) reported that 6 cases of megaloblastic anemia had resulted from primidone therapy. Christenson *et al.* (1957) also reported 2 cases of primidone-induced anemia. It is clear that repeated examination of the blood is desirable during primidone therapy.

Primidone is available in 0.25-gm. tablets. The dosage schedule begins with a low dose of ½ tablet daily, and may be increased weekly if necessary until a daily dose of 2 gm. is reached. The drug does appear to be of greatest value in *grand mal seizures* and has a useful place in the treatment of a segment of grand mal patients.

**Phensuximide (Milontin).** From a series of succinimide substitution compounds synthesized by Miller and Long (1951), Chen *et al.* (1951) found Milontin the most effective anticonvulsant agent against induced seizures in animals. The structure is shown in the formula:



Phensuximide
Milontin
(N-methyl-α-phenylsuccinimide)

Milontin is a white, crystalline powder which is only slightly soluble in water, but readily soluble in alcohol.

*Pharmacologic action.* Milontin was found to be especially effective in combating pentylenetetrazol-induced seizures in rats. Chen and Ensor (1953) observed that diphenylhydantoin alone or with Milontin was ineffective against pentylenetetrazol-induced seizures in rats. The 2 drugs together additively antagonized electrically-induced seizures in animals. They deduced that the 2 drugs functioned separately on the brain, suppressing seizures, and this suggested the possible value of combination therapy in the treatment of mixed grand mal-petit mal seizures. Milontin was shown to exhibit a low order of toxicity in laboratory animals.

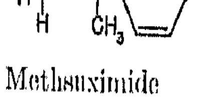
Milontin is absorbed from the gastrointestinal tract in man. Maximal blood levels are obtained 1 to 2 hours after a single oral dose. At the end of 24 hours the drug completely disappears from the blood. Human urine was found to contain 2 metabolites of Milontin resulting from hydrolysis and rupture of the succinimide ring.

*Therapeutic use.* The principal use of Milontin is in the treatment of the petit mal type of epilepsy. Zimmerman (1951) found Milontin to be as effective as trimethadione in the treatment of petit mal; side effects were few. Other observers have experienced success in a segment of their patients treated with Milontin. For example, Millichap (1952) found significant improvement in about 50 per cent of his patients. Doyle *et al.* (1953) had little or no success with the drug in the treatment of 21 children with petit mal epilepsy.

Somnolence and skin eruption have been noted during treatment with Milontin. Millichap (1952) observed toxic side effects in 13 of 21 patients, 10 of whom showed evidence of glomerulotubular damage. One must be warned to take the precaution of frequent urine and blood examinations of patients using this drug. It appears that the place of Milontin as a successful competitor to trimethadione in the treatment of petit mal epilepsy remains to be established.

Milontin is administered according to the patient's needs. Initially 0.5 gm. to 1 gm. 2 or 3 times daily is given. Average daily dose is 1.5 gm., with a maximum of 3 gm.

**Methsuximide (Celontin).** Celontin is a newer anticonvulsive agent used in the treatment of petit mal and psychomotor epilepsy. Chemically it is closely related to Milontin. Its structure is shown in the following formula.



Methsuximide
(N-methyl-α,α-methylphenylsuccinimide)
Celontin

Celontin is a white, crystalline powder, soluble in ether and alcohol but insoluble in water, with a very disagreeable taste.

*Pharmacologic action.* Celontin has been shown to afford effective protection against pentylenetetrazol-induced convulsions when administered orally to rats and mice. It was less effective in protecting cats and mice against supramaximal electroshock convulsions. The acute toxicity of Celontin is low. Depression of the central nervous system is a dominant symptom of Celontin at high dosage levels. The drug was well tolerated by laboratory animals in chronic feeding studies. Some centrilobar damage was observed in the livers of mice and rats fed Celontin. The lesions were considered to be reversible. Studies of other organs revealed no significant pathologic findings.

*Clinical use.* Zimmerman and Burgemeister (1954) used Celontin in the treatment of petit mal epilepsy. They reported that a high degree of anticonvulsive activity was elicited by the drug. The same investigators (1955) considered Celontin a most useful agent in the control of petit mal seizures in 72 patients. The average daily dose was 0.9 to 1.2 gm. Celontin is available in 0.3-gm. capsules.

In psychomotor epilepsy, Zimmerman and Burgemeister (1954) found that Celontin provided improvement in 12 of 15 patients. Livingston and Pauli (1957) treated 136 epileptic patients, mainly children, with Celontin for 6 to 15 months. Maximal dosage schedules of other anticonvulsives had proved ineffective in controlling seizures in 85 of these patients. Daily doses of 300 mg. to 3.6 gm. were used. Celontin was found effective in controlling minor motor and psychomotor seizures. Frequency of seizures was reduced in petit mal epileptics, but grand mal seizures were not successfully controlled by Celontin. The most frequent side effect encountered was drowsiness. No serious, irreversible toxic findings were observed.

The side effects encountered with Celontin are *drowsiness, ataxia, vertigo, vomiting, constipation, diarrhea, periorbital hyperemia,* and *leukopenia. Confused behavior* has also been reported.

**Ethosuximide (Zarontin).** Zarontin is another succinimide derivative that is useful in the treatment of petit mal epilepsy. Chemically it is 2-ethyl-2-methyl-succinimide. It is a white, waxy solid that is insoluble in water.

Chen *et al.* (1951) studied a series of substituted succinimides for their protective action against pentylenetetrazol-induced seizures in animals. These studies led to the use of phensuximide (Milontin) and methsuximide (Celontin) in convulsive disorders. Their value in petit mal epilepsy is limited. The highly protective action against these induced seizures evoked by ethosuximide (Zarontin) prompted its use in the treatment of petit mal epilepsy.

*Clinical use.* Zarontin has been found to be effective in the control of petit mal epilepsy. Although the drug is comparatively new, it appears to be promising. For example, Goldensohn *et al.* (1962) treated 100 cases of epilepsy with Zarontin, of which 62 per cent were petit mal, 18 per cent were petit mal with other seizure types, and 20 per cent were atypical short attacks. They found Zarontin superior to methsuximide, with a greatly reduced incidence of side effects. Of special significance is the fact that in a controlled series of 75 patients Zarontin was found to be superior to trimethadione. Indeed, their results with Zarontin in petit mal compare favorably with the results of most investigators with trimethadione.

The side effects of Zarontin that have been reported are *nausea, vomiting, depression, vertigo, headache,* and *skin rash.* Often these untoward effects subside when the dosage is diminished. It appears that up to the present no blood dyscrasias have been reported. The incidence of side effects is low as compared with the effectiveness of the drug.

Zarontin is available in 250-mg. capsules. For adults and children over 6 years of age the initial recommended dosage is 250 mg. twice daily. The daily dosage may be increased in increments of 250 mg. until either seizure control is achieved or a maximum daily dosage of 1 to 1.5 gm. has been administered.

**Amino-glutethimide (Elipten).** This anticonvulsive agent is chemically related to the hypnotic glutethimide (Doriden) (see page 447). It differs from glutethimide by the substitution of an amino group on the *para* position of the benzene ring. The compound occurs as a white or creamy white, crystalline powder that is almost insoluble in water.

Amino-glutethimide differs from glutethimide pharmacologically in that it mainly depresses the motor cortex and evokes a nonsignificant depressant action on the sensory cortex.

*Clinical use.* There have been only limited clinical trials with amino-glutethimide. It appears to be of some value in grand mal, petit mal, psychomotor, myoclonic, and mixed epileptic seizures. Carter (1960) found amino-glutethimide more effective in grand mal seizures than in petit mal. In petit mal, the drug favorably influenced the electroencephalographic pattern. He found the compound most effective when used in combination with other anticonvulsive agents. This was particularly true with diphenylhydantoin sodium. Pearce (1960) reached similar conclusions with regard to the effectiveness of amino-glutethimide. It appears that the drug has a place as adjunctive therapy with other agents in controlling seizures.

The most frequent side effect of amino-glutethimide therapy is *skin rash. Drowsiness, ataxia,* and *mental confusion* have been reported when the daily dosage exceeds 1500 mg. *Transient leukopenia* has also been encountered. This side effect is rare and reversible upon discontinuance of therapy.

The compound is supplied in 125- and 250-mg. tablets. The usual maintenance dose is 750 mg., although in some cases 1500 mg. is tolerated. The maintenance dose should be established gradually, and if the dosage level is 750 to 1000 mg. daily when seizures are controlled, the schedule should be lowered gradually, if possible.

## THE BROMIDES

The salts of hydrobromic acid, the bromides, have been used in medicine for almost a century. The bromide ion is a depressant to the central

nervous system. It affects mainly the sensory and motor areas of the cerebral cortex. The depressant action of bromides is due entirely to the bromide ion. When bromine is combined with organic radicals which do not produce bromide ions, the characteristic response of bromides is not elicited. Such inorganic compounds as sodium bromate $NaBrO_3$ and sodium hypobromite NaBrO, which produce oxybromide ions, do not evoke the characteristic bromide effect. Furthermore the bromides of sodium, potassium, ammonium, lithium, calcium, and strontium, all of which have been used in therapy, elicit the depressant effect of the bromide ion. It is apparent that no useful therapeutic end can be accomplished by using a variety of salts of hydrobromic acid. When one employs bromide, he is concerned with the depressant action of the bromide ion. This is obtained with least concomitant cation effect from sodium bromide. Therefore sodium bromide is the bromide of choice.

**Sodium Bromide, N.F.** Sodium bromide is a white, crystalline salt. It absorbs moisture from the air but does not deliquesce. It is soluble in 1.2 parts of water and in 16 parts of alcohol.

**Absorption, fate, and excretion of bromides.** Soluble bromides are absorbed readily from the gastrointestinal tract. In high concentration or in tablet form they produce gastric irritation. They are most satisfactorily given well diluted with water.

The bromide ion circulates in the blood and is very slowly excreted by the kidney in the urine; 20 to 30 days may be required for the complete excretion of the bromide ion after a single dose of 1 gm. of sodium bromide. Like the chloride ion, the bromide ion readily permeates the membrane of the red blood cell but not other cell membranes. The bromide ion produces its effects by its presence in the extracellular fluid.

**Bromide-chloride equilibrium.** In the treatment of epilepsy with sodium bromide, the bromide concentration of the body may equal $\frac{1}{5}$ to $\frac{1}{3}$ of the total halogen content. The kidneys appear to be blind to the presence of the bromide ion in the blood, and chlorides and bromides are excreted indifferently. Thus if an individual taking sodium bromide excretes daily 8 to 10 gm. of sodium combined with chloride and bromide, about 10 per cent, or 1 gm., is sodium bromide; if the sodium chloride intake is decreased, the total halogen excreted is diminished, and the amount of bromide excreted is correspondingly reduced. On the other hand, if the individual ingests an additional 10 gm. of sodium chloride, the total halogen excreted is increased and more bromide is eliminated.

This bromide-chloride equilibrium in the blood and tissues affords an explanation for the use of a salt-restricted diet when bromide is used in therapy for long time periods. Obviously, it reduces the dosage schedule of bromide for the patient. Furthermore, in bromide intoxication the administration of sodium chloride will facilitate the excretion of the bromide ion and expedite recovery.

Owing to the fact that the bromide ion may replace the chloride ion in the blood and tissues, the question has arisen as to whether or not the effect of bromide on the cortex is due to chloride deprivation. Hiatt (1939) replaced one-half of the total chloride in dogs and cats by the nitrate ion without producing symptoms of central nervous system depression. Amberson *et al.* (1938) observed that when attempts were made to deprive the body of the chloride ion, the brain held the chloride ion most tenaciously. It appears, therefore, that bromide depression of the cerebral cortex cannot be considered as a result of chloride deprivation, but on the other hand it must be looked upon as a specific response elicited by the bromide ion.

Further evidence to support this view was presented by Czerwinski (1958). She observed in rabbits and dogs that blood-bromide levels were elevated in animals after the withdrawal of bromide administration for short periods of time. The levels dropped more promptly upon chloride administration. Fluctuations in bromide levels during excretion were considered as evidence that bromide toxicity is related to total bromide extracellular retention rather than to the replacement of $Br^-$ by $Cl^-$. Likewise Rosenblum (1958) found no significant relationship between the bromide blood level and the first appearance of physical signs of intoxication in dogs. He suggests further that weight loss encountered in some dogs with undiminished food intake may indicate diminished absorption of nutrients caused by bromide ions.

Wallace and Brodie (1939) showed that the wet tissue/serum ratios of bromide and chloride were in close agreement for all tissues except the brain. On the cerebral cortex, where bromide ions evoke their response, the concentration of the ion was found to be the lowest.

The bromide ion is normally present in the blood to a limited extent. Bromine is a ubiquitous element. It is generally found associated with chlorine. It has been estimated that the normal blood level of bromide ($Br^-$) is 0.33 to 1.73 mg. per cent (Wikoff *et al.*, 1939).

**Action of bromide on the brain.** In man 1 to 3 gm. of sodium bromide produces a feeling of lassitude. There is unconcern, aloofness, and imperturbability. Mental alacrity is depressed. Concentration is impaired, and even mental confusion may result.

There is no effect upon the pain centers. Bromides do not evoke sleep in many individuals. However, sleep often follows the feeling of somnolent passivity produced by the drug.

The effect is not confined to the mnemonic areas of the brain. Where hyperexcitability of the motor cortex is present, as in epilepsy, bromides reduce the number and the severity of the seizures. Bromides antagonize the convulsions produced by camphor and cocaine which originate in the cerebrum and midbrain. The spinal convulsions elicited by strychnine are not effectively combated by bromides. Merritt *et al.* (1937) were able to increase the threshold to electrical stimulation of the motor cortex of the cat 50 per cent by the administration of bromide. The quantity of bromide required, however, was so great that the animal lost coordination of its legs. An amount of phenobarbital sufficient to produce this syndrome will increase the threshold of the motor cortex to electrical stimulation 3- to 4-fold.

**Untoward effects of bromides.** The prolonged ingestion of bromides gives rise to a variety of untoward effects. Gastrointestinal distress is often encountered. *Fetid breath, brown, furred tongue, constipation*, and *flatulence* follow in the wake of the gastrointestinal disorder. In other cases the principal symptoms are *conjunctivitis, lacrimation, coryza*, and *salivation*. The skin rash produced by bromides generally occurs after the foregoing effects. The bromide rash is indistinguishable from acne. It is believed to be the result of bromide in the skin, from which small quantities of bromine have been liberated, causing the irritation. Seborrheic individuals appear to be more susceptible to this symptom of *bromism* than other individuals.

The appearance of these untoward effects of bromide indicates that the drug should be discontinued or the dosage schedule reduced. If the syndrome of bromism is quite distressing, bromide may be rapidly removed from the blood and tissues by the ingestion of large amounts (5 to 10 gm. daily) of sodium chloride.

Several studies have been conducted to reevaluate the chronic toxicity of bromide. For example, dogs were fed sodium bromide 23 mg./kg. for a period of 3 months. Extensive studies were made before and after the feeding period. They showed no significant changes in blood chemistry or hematologic picture after bromide. In addition, there were no positive electrocardiographic findings in the animals. However progressive bromide intoxication in dogs was shown to be accompanied by a decrease in volume of the extracellular space, and in the terminal stages, by hemoconcentration. Certain animals exhibited transient anemia and leukocytosis, and nearly all dogs showed an accelerated sedimentation rate (Rosenblum, 1958).

**Toxic psychosis caused by bromides.** The presence of bromides in the blood of a segment of patients admitted to psychiatric hospitals precipitated an intensive study of the effect of repeated bromide dosage on the behavior pattern.

Millikan and Paul (1946) reported toxic reactions in 36 patients with neurologic and psychiatric disorders who received large doses of sodium bromide for extended periods. The patients were given 3 to 10 gm. of sodium bromide daily. Eight patients who received 3 to 4 gm. daily had low blood-bromide levels and showed no psychic reactions.

In 11 patients the blood-bromide level was 195 to 319 mg. per cent. These individuals were drowsy and their intellectual powers were depressed. There was a slurring of the speech, an unsteady gait, and a generalized clouding of consciousness.

In 9 patients toxic delirium and hallucinations occurred. The blood-bromide levels of these patients were 218 to 330 mg. per cent. All of these patients in which the psychosis developed had some pre-existing personality defect. Patients with organic disease were able to tolerate much higher doses of bromide without showing the psychotic syndrome. The psychotic symptoms disappeared as the blood-bromide level diminished with the withdrawal of the drug. Six patients of the group did not return to the normal mental behavior pattern until the blood-bromide level was below 100 mg. per cent. None of the patients showed signs of habituation to the drug.

It appears that bromide is capable of producing marked changes in the personality pattern of individuals if taken in sufficient quantities to produce blood-bromide levels more than 200 mg. per cent. However, Paskind (1934) and others are of the opinion that bromides produce deleterious effects only in individuals with a preexisting mental defect.

In view of the uncertain value of bromide as a sedative and the frequency of untoward side effects, the drug should be limited to rare cases of epilepsy in which the seizures are not controlled by other drugs.

*Therapeutic uses of bromides.* The principal use of sodium bromide in medicine is to produce *sedation*. For this purpose bromides today are being rapidly replaced by phenobarbital or meprobamate. Bromides are used in the treatment of epilepsy. They control the seizures in a limited number of individuals where other anticonvulsant drugs are ineffective. Bromides are infrequently used to supplement other anticonvulsant drugs in the control of epilepsy.

### THE ANTICONVULSIVE DRUGS IN EPILEPSY

The disease of epilepsy is as old as the written pages of the history of mankind. The convulsive seizure, the sinister cry, the loss of consciousness can be traced back to the earliest annals of medical lore. Paracelsus described epilepsy as the "disease of lightning" because the individual was struck down, as it were, by a bolt from the sky.

The first step that placed the treatment of the disease on a controllable basis was founded upon an erroneous concept with regard to its etiology. Sir Charles Locock in 1857 gave large doses of bromides to 14 epileptic patients, upon the premise that epilepsy was due to onanism, and bromides had been established as eliciting an anaphrodisiac effect. In nearly all of his cases bromides diminished the frequency of the epileptic seizures and their severity.

From that day until 1912 no real advance was made in the therapy of epilepsy. It was established that the bromide ion was responsible for depression of the hyperexcitability of the motor cortex and that bromine in organic molecules was no substitute for ionizable bromides. Further, no bromide salt was found to be superior to sodium bromide, and with that knowledge the therapy reposed until the work of Guelpa and Maria in 1912.

These investigators demonstrated that an acidotic diet would diminish the severity of epilepsy. It was found that acetone and $\beta$-hydroxybutyric acid, which are formed as degradation products of fatty acid molecules in acidosis, are depressant to the motor cortex and thus suppress the symptoms of the disease. This work was confirmed by Wilder (1921). Although the observation was of theoretical interest, the practical application of the acidotic diet was surrounded with innumerable difficulties and also hazards to the patient.

In 1912 in Hoche's clinic in Freiberg, Hauptmann showed that the then new barbiturate *Luminal* (phenobarbital) could be used as successful therapy in epilepsy. Advantages of this new treatment were that no salt-restricted diet was necessary, as is desirable in bromide therapy, and there was no gastrointestinal distress from the ingestion of too much bromide. How the introduction of a phenyl group in the barbituric acid nucleus confers upon the molecule a greater power to depress the hyperexcitability of the motor cortex remains an unsolved problem.

The advantage of phenobarbital over bromide therapy can be easily demonstrated. If one gives a cat bromide in sufficient quantity to produce a lassitude so great that it is difficult for the animal to walk, the threshold to electrical stimulation of the motor cortex is increased approximately 50 per cent. If, on the other hand, the same syndrome of depression is produced by phenobarbital, the threshold to electrical stimulation of the motor cortex is trebled or even quadrupled.

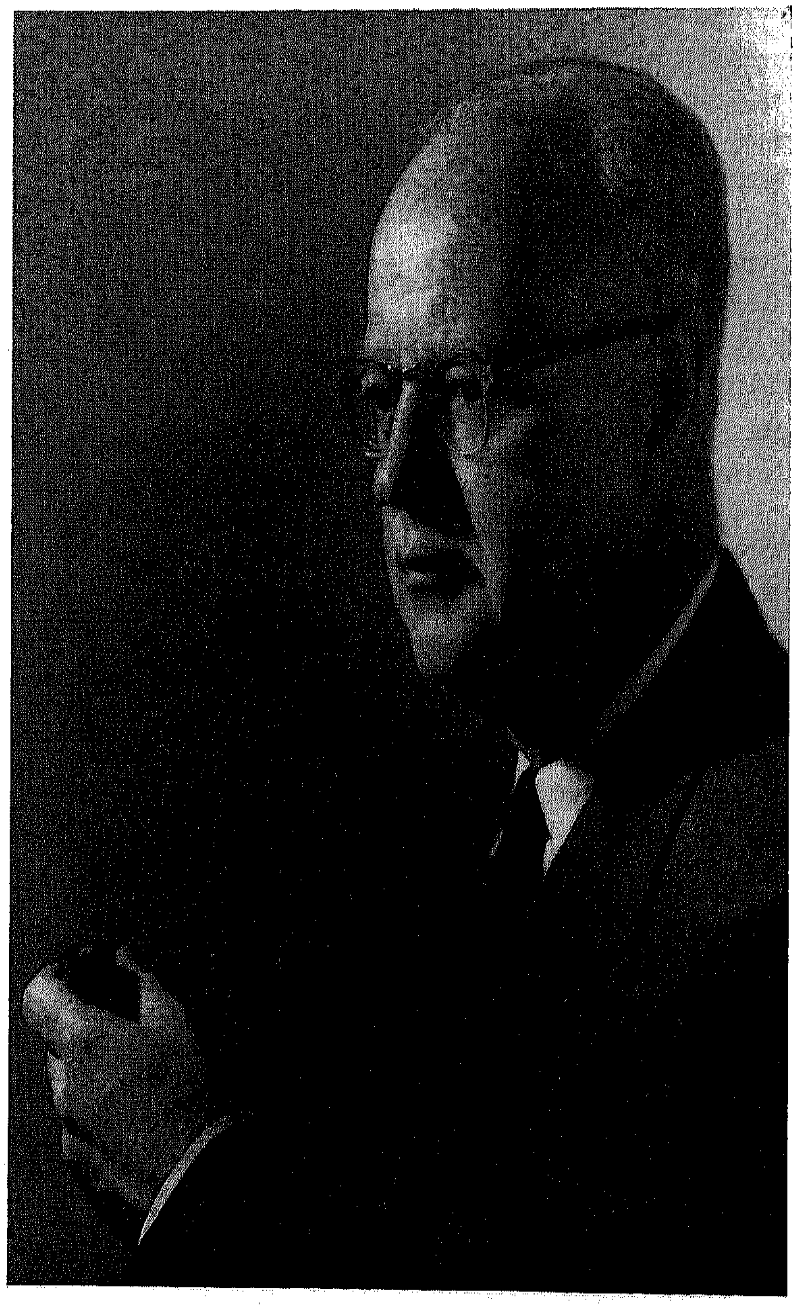
Nevertheless bromide and phenobarbital therapy each presented the problem of depression of sensory areas of the brain simultaneously with sedation of the motor areas.

The next great advance in therapy was made in the decade 1930 to 1940 when a large number of compounds related to the barbiturates, some of which had been prepared by Arthur Dox and Lester Yoder (1921), were reviewed. Those which had not produced sedation and hypnosis had been discarded by these relatively early workers in the field. One of these compounds was found to depress only the motor cortex and not the somesthetic areas of the brain. The compound is diphenylhydantoin sodium, and its relationship to phenobarbital can be observed from the formulas on page 414.

Diphenylhydantoin offers the special advantage of possessing a specificity for the motor cortex while not affecting the sensory areas of the brain to any appreciable extent. Thus with this drug it became possible at last to treat epilepsy without producing dullness of apprehension, lethargy, and lassitude, which so frequently accompany bromide and phenobarbital therapy.

During the decade of diphenylhydantoin therapy, the use of the electroencephalograph had become more general. The brain-wave patterns of grand mal and petit mal epilepsy have become diagnostic. Furthermore, it has been shown that with drugs the cortical dysrhythmia of epilepsy can be corrected. Lennox (1943) showed that the brain patterns of the epileptic as shown by the electroencephalogram were diagnostic. The brain pattern does not appear to be hereditary, but the predisposition to the pattern is likely to be inherited. The dysrhythmia is not a fixed trait and can be modified by the administration of the anticonvulsive drugs.

H. Houston Merritt (1948), distinguished for his clinical investigations in the field of clinical epilepsy, very cogently stated: "The electroencephalogram has given us a brief glimpse behind the scenes, but what is seen in the electroencephalographic tracing is the storm and not the earthquake or other mighty forces which produce the storm."



H. HOUSTON MERRITT

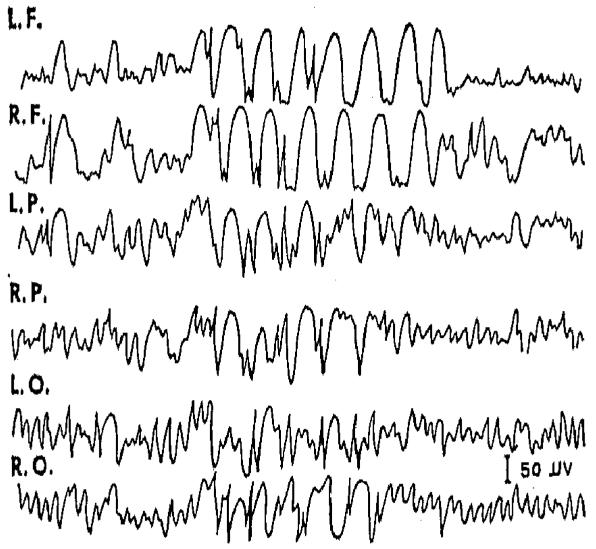
*Distinguished American investigator in the treatment of epilepsy*

"The electroencephalogram has given us a brief glimpse behind the scenes, but what is seen in the electroencephalographic tracing is the storm and not the earthquake or other mighty forces which produce the storm. Until such time as we discover the nature of these forces and learn how to subdue them we will always have failures in the treatment of epilepsy."

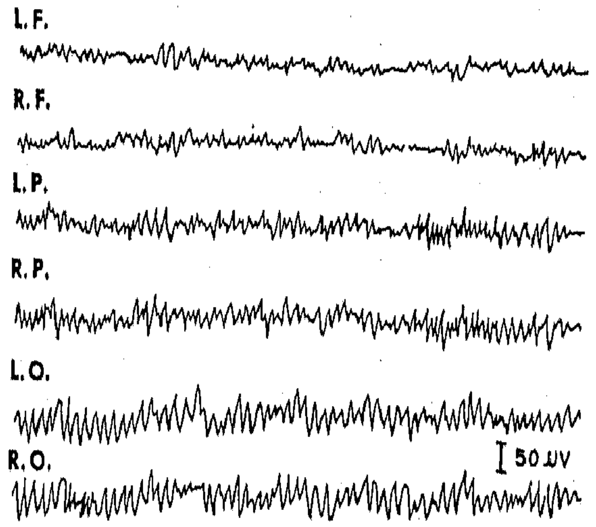
Phenobarbital and bromide remove the characteristic brain dysrhythmia of epilepsy. Dilantin improves the electroencephalogram pattern only slightly, but the general improvement of the patient is greater than the record of the brain waves would indicate.

The next striking advance in the field of therapy in epilepsy occurred in 1944, when Everett and Richards produced trimethadione, useful in petit mal, psychomotor, akinetic, and myoclonic forms of epilepsy. Figure 27-1 shows the effect of trimethadione on the electroencephalogram of a patient with essentially petit mal epilepsy (Lennox, 1945).

Another approach to the treatment of epilepsy is the use of the inhibitor of carbonic anhydrase, Diamox (acetazolamide) (see page 803). This drug was introduced first as a nonmercurial diuretic and was later employed with varying degrees of success in epilepsy. Beneficial results in epilepsy with this drug are not associated with depressant action of the motor cortex, as the compound does not elicit this response. Its capacity to reduce seizures may be associated with the diuresis which it elicits, because of incipient



Before trimethadione: patient has had only 1 or 2 grand mal seizures in her entire life but has had 100 or more petit mal attacks per day. The electroencephalogram shows frequent three-per-second wave-and-spike discharges of the petit mal type. The background activity is slightly fast.



On trimethadione (1 capsule t.i.d.) for 11 days: no grand mal, no petit mal attacks. The electroencephalogram shows no spontaneous seizure discharges, and none could be elicited with hyperventilation. The background activity is still moderately fast.

FIG. 27-1. Effect of trimethadione on the electroencephalogram in petit mal epilepsy. (From W. G. Lennox, J. A. M. A., **129:** 1069, 1945.)

acidoses produced, or perhaps because of the inhibition of carbonic anhydrase in neuronal tissue. This treatment has been tried in various clinics as the principal drug or as adjuvant support to the classical anticonvulsive drugs. Lombroso *et al.* (1956) studied 126 patients under acetazolamide therapy for periods of 3 months to 3 years. In 37 per cent of the cases the seizures were reduced by at least 90 per cent; in others it was less effective; nevertheless, significant suppression of seizures was noted. The different variants of the disease responded to the treatment. The degree of improvement did not appear to be related to a personal history of brain injury, a family history of epilepsy, or the type of seizure. This is an interesting approach to the treatment of this disease, and it should further elucidate the role of acidosis and carbonic anhydrase in the metabolism of normal and abnormal neuronal tissue.

Many laboratory procedures have been developed to screen drugs for anticonvulsive activity. Furthermore, these methods are valuable in assessing the relative clinical usefulness of these drugs in epilepsy. The agreement between the laboratory tests and the clinical efficacy appears to be fairly reliable. Electric shock convulsions in animals are controlled best by those drugs which are most useful in the grand mal type of epilepsy. The pentylenetetrazol convulsion in animals is best combated by drugs which are efficacious in controlling the petit mal type of epilepsy. Another laboratory method developed by Toman *et al.* (1946) is useful in screening many different types of compounds for anticonvulsive activity. The method depends upon electrical stimulation of the cortical activity of the mouse or rat. The extensor component of the tonic phase of the convulsion is observed. The anticonvulsant is given, and after a period sufficient to permit absorption, the amount of drug required to abolish the extensor tonic seizures in 50 per cent of the animals is determined.

Of further interest are the observations of Esplin *et al.* (1957 *et seq.*), discussed on page 414, concerning the effect of the anticonvulsive drugs on spinal cord synaptic transmission. For example, it was stated previously that diphenylhydantoin had a marked effect in depressing post-tetanic potentiation but only a mild action in decreasing the response to repetitive stimulation. On the other hand, trimethadione's action was most marked in decreasing response to repetitive stimulation, while exhibiting no depression of post-tetanic potentiation.

In the treatment of the various manifestations of epilepsy the physician now has many useful and specific drugs at his disposal. Merritt (1948) states: "Failure to administer the proper dosage is more common than the incorrect use of drugs. The dose of an anticonvulsive drug for epileptics cannot be standardized anymore than that of insulin for the diabetic. The dosage must be determined for each individual patient."

The determination of the most suitable anticonvulsive drug often requires months of trial. It is most desirable to inaugurate therapy with a well-established drug that manifests the least untoward effects. Fixed formulas for therapy are difficult to establish. Anticonvulsive therapy must be tailor-made (Bercel, 1952).

From the data available the authors are of the opinion that the drug of choice in *petit mal* epilepsy is *trimethadione.* Experimentally it has a higher protective index against pentylenetetrazol-induced seizures; clinically it has been proved of value for more than a decade. In addition, the incidence of toxic manifestations is low.

Several clinical investigations have reported that ethosuximide (Zarontin) is as efficacious in petit mal as trimethadione. Side effects with ethosuximide are few and not serious. It is probable that this drug will be a strong competitor to trimethadione and perhaps will supersede it as the drug of choice.

In *grand mal* epilepsy diphenylhydantoin alone or diphenylhydantoin with *phenobarbital* appear to be the most effective drugs in a large segment of the cases, with minimal side effects. Weaver *et al.* (1955) studied the protective index in rats of combinations of these two drugs against electrically-induced seizures. Their data indicate a period of "coaction" between the two drugs which gives maximal protection more potent than that calculated on the basis of similar joint action of the component drugs. They favor a dosage of 67.5 per cent phenobarbital and 32.5 per cent diphenylhydantoin. Several clinical observers, however, achieved best results by using higher percentages of diphenylhydantoin than those of phenobarbital. Of special interest is the work of Wapner *et al.* (1962) in their studies of phenobarbital medication on the learning process in children. They found that epileptic children whose seizures were controlled

by phenobarbital did not vary significantly in their learning behavior from other children of similar age, sex, race, and intellect.

Gruber *et al.* (1961) found the following degrees of effectiveness for various drugs in suppressing motor seizures in epilepsy and focal brain damage: equal degrees of effectiveness were found for phenobarbital, 30 mg.; diphenylhydantoin, 93 mg.; metharbital, 110 mg.; methylphenylethylhydantoin, 112 mg.; mephobarbital, 128 mg.; and primidone, 200 mg. They observed also that 70 mg. of diphenylhydantoin and 470 mg. of Peganone (ethotoin) were equally effective. The more comparative studies that are conducted, the more apparent the effectiveness and comparative safety of phenobarbital becomes.

If success in grand mal epilepsy is not achieved with diphenylhydantoin-phenobarbital combinations, Mesantoin should be considered as a well-tried and effective anticonvulsant drug. It must be remembered that the treatment of epilepsy is a long-term investment in drug therapy. Therefore the hazards of chronic toxicity must be carefully considered. Within the last few years two anticonvulsant drugs have been withdrawn because of delayed chronic toxicity. The physician should therefore be urged to allow the newer drugs to be investigated over very long periods of time in the hands of specialists before using them in place of the established anticonvulsives.

The principal drugs used for the treatment of epilepsy are shown in table 27-2 with their indications, dosage, and side effects (Chao, 1963).

### The Biochemical Lesion in Seizures

Recent years have witnessed fundamental studies designed to unravel the biochemical lesion involved in epilepsy. The comprehensive studies of Tower (1955 *et seq.*) have revealed interesting differences in the biochemical constituents of epileptogenic and nonepileptogenic portions of the cerebral cortex. These findings are shown in table 27-3.

The data show that the acetylcholine system, glutamic acid, and electrolyte metabolism are altered in the epileptogenic cortex. The metabolic defects are reversible *in vitro.* The systems involved are concerned with the energy metabolism of the cell. Intimately associated with Krebs' cycle of intermediary carbohydrate metabolism is glutamic acid. This acid, together with glutamine, constitutes the major portion of the intracellular nonprotein nitrogen of nerve tissue. The use of glutamic acid in seizure treatment has been recognized for some time. Methionine sulfoximine, a convulsant agent, has been shown to inhibit glutamine synthesis. Glutamic acid was found to be ineffective in producing normal cerebral glutamic acid concentrations *in vitro.* Its lack of success in the treatment of seizures appears to be due to its failure to cross the blood-brain barrier. However, glutamine and asparagine are effective in correcting the glutamic acid levels in the epileptogenic cortex *in vitro.*

It appears that seizures are associated with a distortion of the metabolism of acetylcholine, glutamic acid, and potassium. It has been shown that certain anticonvulsive drugs affect these facets of neuronal metabolism. For example, phenobarbital has been shown to increase significantly the bound acetylcholine content of cortical slices of the cat. Barbiturates also appear to protect the neuronal cells from the loss of glutamic acid and potassium ions. As previously stated, diphenylhydantoin evokes a loss of cerebral intracellular sodium. Acetazolamide appears to stabilize intracellular potassium and to diminish the penetration of sodium ions. All of these effects are consistent with the correction of the biochemical lesion of the seizure.

Based upon these provocative studies of Tower (1955 *et seq.*), glutamine and asparagine were studied in epileptic patients. The agents were administered in large doses: for example, 12 gm. of asparagine were given 5 times daily to a 14-year-old boy. The results in most cases were promising, confirming the biochemical studies *in vitro.* Neither glutamine nor asparagine elicit any effect *in vitro* or *in vivo* on normal nerve tissue. These compounds are not drugs foreign to neuronal metabolism. The control of experimentally-induced seizures, as well as clinical epilepsy, by asparagine and glutamine are likely to be related to a restoration of glutamic acid metabolism to normal.

They are the first substances administered to epileptics with promising results, the indication for which was derived from studies on the human epileptogenic brain. This study appears to us to be a milestone of progress in unravelling the mystery of the epileptic seizure. At long last the biochemical lesion responsible for the cortical dysrhythmia is becoming unmasked.

TABLE 27-2

*Drugs for Use in Epilepsy* (Modified from D. Chao, 1963).

| Drugs | Indications | Dose | Toxicity | Preparations |
|---|---|---|---|---|
| | | *mg./kg./day* | | |
| Celontin (methsuximide) | Psychomotor, akinetic, and myoclonic seizures; massive spasms | 15 to 20 | Drowsiness, ataxia | 300-mg. capsules |
| Diamox (acetazolamide) | All types of seizures | 15 to 30 | Loss of appetite, acidosis, numbness of extremities | 250-mg. tablets; 250 mg. per 4 ml. suspension; 500-mg. ampules i.v. or i.m. |
| Dilantin (diphenyl hydantoin) | Any seizure with the exception of lapse, myoclonic, and akinetic attacks | 3 to 8 | Gum hypertrophy; ataxia, diplopia, nystagmus; rash and fever, nausea and vomiting; hirsutism | 30-mg. capsules; 50-mg. Infatabs; 100-mg. capsules; 100-mg. D.A. Kapseals; 25 mg. per ml. suspension (*i.e.*, about 1.5 mg. per drop); 250-mg. Steri-Vial with diluent in ampule |
| Elipten (aminoglutethimide) | Non-petit mal seizures | 10 to 20 | Sleepiness; skin rash | 250-mg. tablets |
| Gemonil (metharbital) | Massive spasms, myoclonic seizures, etc. | 5 to 15 | Drowsiness | 100-mg. tablets |
| Meprobamate | Absence attacks and convulsive equivalents; massive spasms | 20 to 40 | Drowsiness; skin rash rarely | 200-mg. tablets; 400-mg. tablets |
| Zarontin (ethosuximide) | Petit mal seizures | 20 to 30 | Skin rash, gastrointestinal distress, headache | 250-mg. gelatin capsules |
| Mesantoin (methyl-phenyl-ethyl hydantoin) | (Same as Dilantin) | 4 to 10 | Rash and fever; leukopenia and agranulocytosis; ataxia | 100-mg. tablets |
| Milontin (phensuximide) | Absence, myoclonic, akinetic | 20 to 40 | Nephrotoxic (slightly) | 0.5-gm. capsules; 65 mg. per ml. suspension |
| Mysoline (primidone) | Generalized, focal, psychomotor attacks | 12 to 25 | Drowsiness; ataxia; skin rash | 250-mg. tablets; 65 mg. per ml. suspension |
| Phenobarbital | Any seizure problem | 1 to 5 | Drowsiness; skin rash and fever; hyperirritability in children | 16-mg. tablets; 32-mg. tablets; 64-mg. tablets; 100-mg. tablets; 4 mg. per ml. elixir |

TABLE 27-2—*Continued*

| Drugs | Indications | Dose | Toxicity | Preparations |
|---|---|---|---|---|
| | | *mg./kg./day* | | |
| Tridione (trimethadione) | Lapse, myoclonic and akinetic attacks; other seizures with EEG patterns of 3 per second generalized paroxysmal bursts | 20 to 50 | Rash; leukopenia and agranulocytosis; photophobia; irritability | 300-mg. capsules; 150-mg. tablets; 37.5 mg. per ml. elixir |

### The Use of Drugs in Paralysis Agitans

Paralysis agitans, or Parkinson's disease, is a chronic malady of the central nervous system, showing characteristic symptoms of *muscular tremor* and *rigidity*. This is accompanied by slowness of movement and muscular weakness. The disease occurs in a segment of the individuals who have suffered with epidemic encephalitis and is hence referred to as *postencephalitic parkinsonism*. It may also be caused by intoxication with carbon monoxide or certain metals such as manganese. Idiopathic parkinsonism occurs in middle-aged or elderly individuals as a cerebral degenerative disease caused by necrosis of cells in the *substantia nigra*, *corpus striatum*, and other areas of the brain. The disease may progress slowly through the years. Mental changes are not usually present, and sensory response is generally unimpaired. The disease may occur in elderly patients as a sequel to advanced cerebral arteriosclerosis. It is estimated that parkinsonism comprises about 8 per cent of the disabling chronic diseases. Doshay (1961) estimates that there are 1.2 million cases of Parkinson's disease in the United States. This number will undoubtedly increase as more people live longer, since at present there is no cure for the disease.

It appears obvious from the nature of parkinsonism that the treatment with drugs is mainly palliative; it is designed to diminish the tremor, reduce the muscular rigidity, elevate the mood of the patient, and prevent the oculogyric crisis of the disease.

For many years belladonna preparations were the only drugs available for the treatment of this disease. Today the alkaloids of belladonna (see page 607), certain synthetic cholinergic blocking agents, certain antihistaminics, and the cerebral stimulant dextroamphetamine are the mainstay of therapy in paralysis agitans.

TABLE 27-3

*Components of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex*

| Sample | Cholinesterase Activity | Cortical Slices Incubated 60 Min. at 27 mM K+ | | | |
|---|---|---|---|---|---|
| | | Change in Bound Acetylcholine* | Level of Glutamic Acid† | Level of Potassium | Level of Sodium |
| | *μL.CO$_2$/g./hr.* | *μg./gm./hr.* | *μM./gm.* | *μEq./gm.* | *μEq./gm.* |
| Nonepileptogenic | 0.95 | +0.55 | 9.9 | 95.5 | 65.5 |
| Focal epileptogenic | 1.25 | 0.0 | 4.75 | 69.5 | 83.0 |

* Free acetylcholine production—no significant differences (1.9; 1.65).

† Glutamine levels—no significant differences (4.8; 5.25).

Atropine and hyoscine are considered most valuable in the control of rigidity (Doshay and Zier, 1953). The synthetic cholinergic blocking agent Cogentin (benzotropine) is considered by Doshay superior to the naturally-occurring belladonna alkaloids.

For use in combating the tremor the alkaloid hyoscine is considered the drug of choice. For prevention of the oculogyric crisis the synthetic cholinergic blocking agent trihexyphenidyl is believed to be the most effective drug. However, there is no consensus.

In order to lift the mood of the patient and combat the akinesia and lethargy, dextroamphetamine is extensively employed.

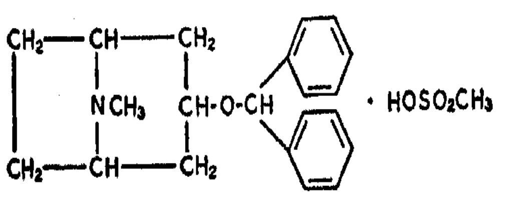
**The use of atropine and hyoscine in paralysis agitans.** A description of the pharmacologic action of these alkaloids is given on page

598. Suffice it to say at this point that their action results principally from their capacity to block the action of acetylcholine. Atropine sulfate tablets are given, 1 mg. 3 times a day. The dose is gradually increased to 3 mg. 3 times a day. Where it is necessary to control the oculogyric crisis, the dose may have to be increased somewhat. In elderly individuals these larger doses of atropine might predispose the patient to glaucoma.

If the patient is excitable and nervous, hyoscine is preferred to atropine because of its depressant cerebral action. The dose of hyoscine hydrobromide in tablets is 0.3 to 0.6 mg. 3 times a day.

Other preparations of the combined belladonna alkaloids are available, such as Rabellon, which is an extract of belladonna root containing in each tablet 0.5 mg. of the active alkaloids.

**Benztropine Methanesulfonate, N.F. (Cogentin).** Benztropine contains in 1 molecule the tropine nucleus and the basic structure of some of the active antihistaminics, as shown in the formula:



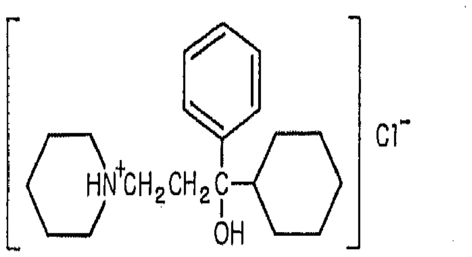
Benztropine Methanesulfonate, N.F.
Cogentin

Benztropine occurs as a white, crystalline powder which is soluble in water.

Benztropine is a potent anticholinergic agent. When employed in Parkinson's disease, it appears to be of value in the control of rigidity and tremor. Edwards (1954) considers benztropine to be among the best single agents used in the control of the disease. The drug is given in tablets of 1 to 2 mg. 3 times a day. Frequently the dose must be reduced if xerostomia is marked. The antihistaminic properties of diphenhydramine are evoked to some degree by benztropine owing to the benzhydryl ether portion of the molecule. Edwards is of the opinion that the effectiveness of benztropine approaches that of the combined therapy with diphenhydramine and belladonna (Rabellon).

Doshay *et al.* (1956), in a comprehensive 5-year study of 302 cases of paralysis agitans, found benztropine gave the best results in the control of rigidity, contracture, tremor, and insomnia. There was little or no increase in tolerance to the drug. He found that benztropine therapy gave the most satisfactory results when combined with dextroamphetamine as a cerebral stimulant. On a dosage schedule of 1 to 4 mg. daily in older patients and 2 to 8 mg. in younger patients, there were no serious side effects. Macular skin rash was encountered in 1 per cent of the patients and xerostomia occurred in about ½ of the group. It appears that benztropine's value in the treatment of paralysis agitans is established. However, its comparative efficacy with other agents used in the treatment of the disease is difficult to assess.

**Trihexyphenidyl, U.S.P. (Artane).** Among the various agents which are used as substitutes for atropine in Parkinson's disease is trihexyphenidyl. Trihexyphenidyl is an antispasmodic which owes its action to its direct relaxant effect on smooth muscle and also to its anticholinergic activity. The structure of trihexyphenidyl is shown below.



Trihexyphenidyl
Artane
(α-cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride)

Various studies on laboratory animals have shown that trihexyphenidyl exhibits about ½ the antispasmodic action of atropine. Other actions compared to atropine quantitatively are: mydriasis, ⅛; antisialogogue effect, ⅛; and cardiovagal inhibitory action, 1/10. Acute and chronic tests on various species of animals demonstrated that trihexyphenidyl exhibited a margin of safety which would permit clinical trial.

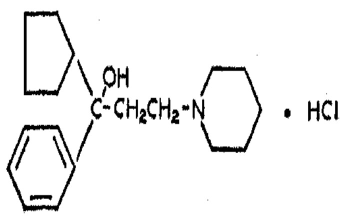
Trihexyphenidyl is especially useful in the treatment of Parkinson's disease. It appears to be of benefit in the postencephalitic as well as the arteriosclerotic and idiopathic types of parkinsonism.

There are several reports of the clinical use of trihexyphenidyl in Parkinson's disease. In the main, the results with the drug were encouraging. Corbin (1949) treated 150 patients suffering from various *dyskinesias* with trihexyphenidyl. Of these, 86 had Parkinson's disease. A high percentage of each group of patients received symptomatic benefit from trihexyphenidyl. Corbin was of the opinion that the results obtained were comparable to or better than belladonna preparations and, furthermore, had fewer side effects. From 30 to 50 per cent of the patients receiving trihexyphenidyl experienced *xerostomia, blurring of vision, dizziness, mild nausea* or, *nervousness.* The symptoms appear to be less severe, however, than with belladonna preparations.

Doshay *et al.* (1954) summarized their experience after 5 years' trial with trihexyphenidyl in the management of over 400 patients with Parkinson's disease. Improvement was noted in 73 per cent on an individualized dosage schedule of 2 to 7.5 mg. daily. It appeared to be valuable in the alleviation of the major symptoms. Combined drug therapy was found necessary in only 30 per cent of the cases. Edwards (1954) is of the opinion that the most successful results with trihexyphenidyl are achieved when combined therapy with it, belladonna, and diphenhydramine is used.

Treatment with trihexyphenidyl is best begun by a gradual dosage increase—1 mg. the first day, 2 mg. the second day, and a gradual increase in the dose until a total of 6 to 10 mg. daily are given. Doses as high as 12 to 15 mg. daily may be required in the postencephalitic type of parkinsonism. Trihexyphenidyl is available in 2- and 5-mg. tablets.

**Cycrimine Hydrochloride, N.F. (Pagitane Hydrochloride).** Pagitane is related to trihexyphenidyl chemically, having a cyclopentyl ring substituted for the cyclohexyl ring in trihexyphenidyl, as shown in the formula:



Cycrimine Hydrochloride, N.F.
Pagitane
(1-phenyl-1-cyclopentyl-3-piperidine-1-propanol hydrochloride)

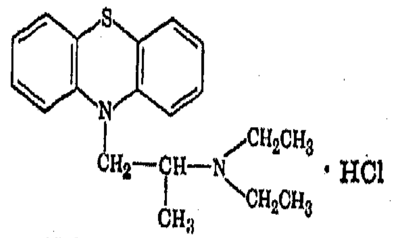
Pagitane is a white, crystalline solid which is slightly soluble in water. Pagitane was employed first as an intestinal antispasmodic, and its close chemical relationship to trihexyphenidyl prompted its use in Parkinson's disease.

Magee and DeJong (1953) observed that in relaxing the gastrointestinal tract Pagitane was about ½ as effective as atropine. It elicits, however, only 1/10 the antisialogogue action of atropine. Pagitane evokes no antihistaminic action. Toxicity studies in laboratory animals indicated a clinical margin of safety.

Several clinical reports show the usefulness of Pagitane in the management of Parkinson's disease. Its action is similar to that of trihexyphenidyl. However, Zier and Doshay (1954) found Pagitane effective in certain cases in which trihexyphenidyl was showing a diminished activity. They observed some slight cerebral stimulation elicited by the drug. These workers consider Pagitane slightly more potent than trihexyphenidyl and also to elicit less xerostomia. It is considered more valuable in the treatment of the *rigidity*, *akinesia*, and *oculogyric crisis* than in the *reduction of the tremor.* The side effects of Pagitane are xerostomia, dizziness, blurring of vision, and nervousness.

Pagitane is supplied in 1.25-mg. tablets. The initial dose is one 2.5 mg. tablet per day and should be increased every 2 or 3 days until effective, in accordance with the patient's tolerance.

**Ethopropazine Hydrochloride (Parsidol).** Parsidol was used first in the treatment of Parkinson's disease in England, Canada, Australia, and France and later introduced in America. It is a phenothiazine derivative as shown in the formula:



Ethopropazine Hydrochloride
Parsidol
[N-(2-diethylamino 1 propyl)- phenothiazine hydrochloride]

Parsidol occurs as a white, crystalline powder which is soluble in hot water. It darkens upon exposure to light.

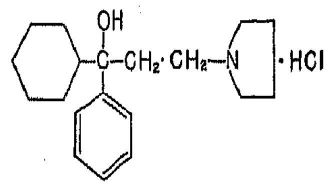
Weese (1954) studied the pharmacology of Parsidol and observed its powerful anticholinergic action. It also elicits *antihistaminic, autonomic ganglionic blocking, adrenergic blocking, central nervous system depression,* and *local anesthetic* actions.

Parsidol, with its multifaceted pharmacologic responses, was studied extensively in Parkinson's disease by Doshay *et al.* (1956) in America. Other English and European investigators had found the drug valuable in the treatment of Parkinson's disease. They used Parsidol in 147 patients exhibiting the variants of Parkinson's disease, whose symptoms had not responded to other therapy. They assert that Parsidol was more effective in the control of the tremor than any other agent. The patients improved in gait, posture, and speech, in addition to enjoying better sleep. Parsidol caused drowsiness and dizziness, but no serious side effects were encountered.

The usual initial dose of Parsidol is 20 to 50 mg. 4 times a day. Increases may be instituted after a few weeks of treatment in the form of 50-mg. increments daily up to 500 mg. daily. Doshay *et al.* found a daily dosage of 150 to 200 mg. optimal.

Doshay and associates (1956) instituted newly-devised electronic recording instruments for objectively measuring rigidity and tremor in Parkinson's disease. By these objective measurements Parsidol therapy showed a 55 per cent improvement in the patients' rigidity. This is a step forward in the evaluation of agents in Parkinson's disease.

**Procyclidine Hydrochloride (Kemadrin).** Kemadrin is another anticholinergic drug used in the treatment of Parkinson's disease. Its structure shows close relationship to certain of the antihistaminics, as indicated in the formula:



Procyclidine Hydrochloride
Kemadrin
(1-cyclohexyl-1-phenyl-3-pyrrolidinopropan-1-ol hydrochloride)

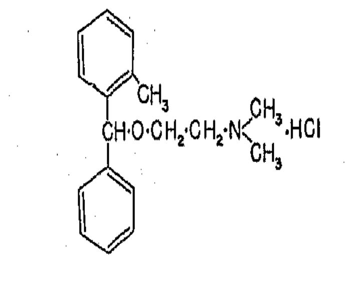
Kemadrin is a white, crystalline powder which is soluble in water.

*Pharmacologic response.* Kemadrin exerts an atropine-like antispasmodic effect on smooth muscle. It antagonizes the spasm elicited by acetylcholine, histamine, barium, or physostigmine. The mydriatic action of Kemadrin is about $\frac{1}{25}$ that of atropine. The antisialogogue action of Kemadrin is also only a small fraction of that elicited by atropine. Small doses of 0.2 mg./kg. given intravenously to dogs evoked no effect upon blood pressure or respiration. The depressor effect of acetylcholine was abolished by Kemadrin. The $LD_{50}$ of Kemadrin to mice intravenously is 60 mg./kg. Subcutaneously, 300 mg./kg. did not elicit a toxic response. Chronic toxicity studies in rats conducted over a 9-week period indicated the availability of Kemadrin for clinical trial.

*Clinical use.* Kemadrin is useful in the variants of Parkinson's disease. It may be employed as a single medication or in conjunction with belladonna preparations. Schwab and Chafetz (1955) used Kemadrin in 87 patients with Parkinson's disease for periods of 3 to 20 months. Approximately half this number responded favorably to the drug. In these patients mood elevation accompanied the relief of rigidity. They state: "Kemadrin may be employed to good advantage in combination with atropine-like drugs." In a series of 52 cases Doshay *et al.* findings paralleled those of Schwab and Chafetz; namely, about half were favorably controlled by Kemadrin. They noted control of tremor and greater mobility.

The optimal dosage of Kemadrin is between 15 and 20 mg. daily in divided doses. In some cases the daily dose may be elevated to 40 mg. With low dosage schedules the side effects are few. Xerostomia and blurring of vision are rare. Gastric disturbance has been encountered but can be minimized by giving the drug with meals. High dosages may produce vertigo and possibly confusion and hallucinations. Kemadrin is available in 5-mg. tablets.

**Orphenadrine Hydrochloride (Disipal).** Disipal is a substituted benzhydryl ether, chemically related to the antihistaminic drug diphenhydramine, which is used in the symptomatic treatment of Parkinson's disease and muscle spasm syndrome. Its structure is shown in the following formula.



Orphenadrine Hydrochloride
Disipal
β-dimethylaminoethyl-2-methylbenzhydryl ether hydrochloride)

Disipal is a white, crystalline powder which is readily soluble in water.

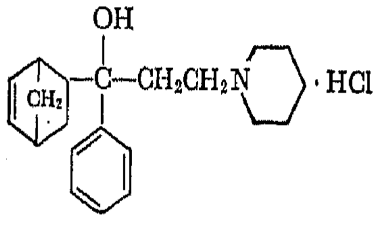
*Pharmacologic action.* The principal pharmacologic action of Disipal is its anticholinergic, antihistaminic, and antitremor activity in skeletal muscle. It differs from diphenhydramine in that it elicits no soporific effect. Disipal is readily absorbed from the gastrointestinal tract and exhibits a low order of toxicity. Chronic studies in various laboratory animals have shown that Disipal evokes no harmful action upon the principal organs or the elements of blood.

*Clinical use.* Disipal was introduced originally for the symptomatic treatment of Parkinson's disease. Doshay and Constable (1957) used Disipal in 176 patients with paralysis agitans in a dosage schedule of 50 mg. 3 times daily. It appeared to be compatible with other currently used anti-Parkinsonism agents. In 98 of these patients, Disipal appeared to be of value in the mitigation of the symptoms of the disease; in some, the beneficial effects were striking. There was relief of objective symptoms such as weakness, fatigue, and depression. Disipal appeared to be least effective in those patients who presented major tremor as a dominant symptom. The percentage of improvement among these patients was higher in the postencephalitic group than in the idiopathic and arteriosclerotic groups. Side effects with Disipal are comparatively few and mild. They generally disappeared when the dosage schedule was reduced. *Mild excitation*, *xerostomia*, *mental clouding*, and *nausea* were among the effects encountered in small segments of the patients. Doshay and Constable state: "Disipal is a harmless preparation, with minimal side actions, and is safe to employ even in cases complicated by glaucoma."

Clinical trials with Disipal in the treatment of musculoskeletal and neurological disorders such as exaggerated natural tonus, spasticity, and low back pain indicate further trial with this agent in these conditions. The dosage schedule is the same as employed in paralysis agitans, namely, three 50-mg. tablets daily. Disipal in the form of its citric acid salt is available under the name *Norflex* for use as a skeletal muscle relaxant. The various conditions of skeletal muscle spasm and pain in which Norflex is indicated are discussed under skeletal muscle relaxants (see page 436).

Norflex is available in 100-mg. tablets; 1 tablet twice daily is the recommended dose.

**Biperidine Hydrochloride (Akineton Hydrochloride).** Biperidine is another anticholinergic agent used in the treatment of Parkinson's disease. From the formula it is observed that chemically it is related to trihexyphenidyl. Each molecule contains a substituted propanolamine group.



Biperidine Hydrochloride
Akineton
α-(bicylo[2·2·1]hept-5-en-2-yl)-α-phenyl-1-piperidinepropanol

Biperidine evokes the typical spasmolytic and antisecretory responses of other anticholinergic agents. Its spasmolytic action is $\frac{1}{25}$ that of atropine, and the antisialogog activity is about $\frac{1}{8}$ of atropine. The mydriatic activity is about $\frac{1}{6}$ of that of atropine.

There appears to be no clinical evidence that biperidine offers any special advantages over the other drugs of this class. Therapy with biperidine is more effective in control of rigidity than tremor. It suppresses salivation and improves the gait. The drug is less effective in the arteriosclerotic form of the disease than in postencephalitic or idiopathic parkinsonism.

The side effects are similar to those encountered with other anticholinergic drugs. They include *xerostomia*, *blurred vision*, *dizziness*, and *gastric irritation*. These effects can usually be controlled by reduction of the dosage schedule. Transient psychotic reactions have also been reported. The usual precautions for anticholinergic agents in glaucoma and prostatic hypertrophy are applicable to biperidine.

Biperidine is available in 2-mg. tablets. The generally recommended dose is 2 mg. 3 or 4 times daily.

**Chlorphenoxamine Hydrochloride (Phenoxene).** This is another drug used in the treatment of Parkinson's disease. Chemically the compound is 2-(*p*-chloro-α-methyl-α-phenylbenzyloxy)-N,N-dimethylethylamine hydrochloride. The drug elicits antihistaminic and anticholinergic activity. The agent resembles the other drugs of this class previously discussed. The side effects of chlorphenoxamine are mainly *drowsiness* and *vertigo*. Although the compound is an anticholinergic, it does not appear to evoke xerostomia or blurred vision. It appears that chlorphenoxamine is most effective in Parkinson's disease when used as adjunctive therapy with other drugs. The dose is 50 mg. 3 times daily and may be increased to 100 mg. 3 times daily.

The availability of various synthetic antispasmodic drugs useful in parkinsonism has materially strengthened the physician's armamentarium, but it is obvious that we await more effective drugs for the symptomatic relief of the disease. What is more, it is quite clear that not all patients are controlled best by any one drug, and that a careful selection of an agent from those available is the duty of the critical therapist. Besides, it is apparent that at present combined medication with two or three drugs will often achieve greater success in some patients than medication with any single agent.

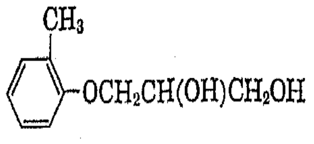
**Surgical treatment of Parkinson's disease.** Surgical methods for the treatment of selected cases of Parkinson's disease have attracted much attention in recent years. Cooper *et al.* (1958) reported a 5-year follow-up study of more than 700 operations; they state that tremor and rigidity are relieved in 80 per cent of properly selected cases, with a mortality risk of 2.4 per cent and a risk of hemiparesis of 3 per cent. At present it appears that the most effective procedure consists of destruction of structures in or near the *globus pallidus* by means of necrotizing chemical agents, ultra-high frequency electromagnetic vibrations, or ultrasonic vibrations. More recently the attack on the basal ganglia has shifted from the globus pallidus to the thalamus with greater safety and apparently better results. The technic now being employed is *cryothalamotomy*. Again, the most favorable results are achieved in younger patients with only unilateral involvement accompanied by good physical and mental health (Doshay and Boshes, 1962).

Despite the dramatic results achieved in selected cases, the pharmacologic approach is indicated in the majority of patients with paralysis agitans.

### Skeletal Muscle Relaxants

Another class of pharmacologic agents has been introduced into the armamentarium within recent years; these are known as skeletal muscle relaxants. They now enjoy a wide field of usefulness in the treatment of *skeletal muscle spasm, acute back pain, bursitis, torticollis,* and to a limited extent in *paralysis agitans.*

**Mephenesin, N.F. (Myanesin, Tolserol).** Berger and Bradley (1946) studied pharmacologically a number of simple mono ethers of glycerol. They found that these substances exhibited qualitatively the same type of response, *i.e.,* relaxation of skeletal muscle. Mephenesin was found to be one of the most potent in the series. Its structure is shown in the accompanying formula.



Mephenesin. N.F.
Myanesin
(3-*o*-tolyloxy-1,2-propanediol)

Mephenesin is a white odorless powder, slightly soluble in water.

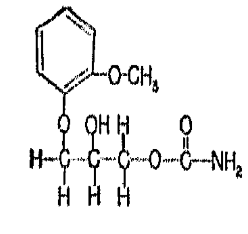
The relaxant action of mephenesin is central, with some slight neuromuscular depression. The sites of depression appear to lie in the midbrain and brain stem at the level of the thalamus and below, and in the spinal cord, perhaps at the internuncial neurons.

Large intravenous doses of mephenesin do not produce significant alteration of the electroencephalogram in man. It appears that the activity of the drug is confined to a depressant effect mainly on the spinal cord. This is manifested by the effectiveness with which it antagonizes strychnine convulsions in laboratory animals.

Mephenesin, however, has found a field of usefulness as a relaxant for spastic and neurological disorders. In these conditions the compound is administered orally and appears quite free from untoward activity. The drug has been used with limited success in *delirium tremens, hemiplegia, paraplegia, multiple sclerosis,* and *arthritis,* in which spasticity of skeletal muscle is a factor. The use of mephenesin in Parkinson's disease has been disappointing. The dose is 1 to 3 gm. 3 to 5 times daily.

*Mephenesin carbamate* (*Tolseram*). The carbamate of mephenesin (Myanesin) is available under the name of Tolseram. The action is the same as that of mephenesin except that the duration of action is longer. The usual dose is 1 to 3 gm. 3 to 5 times daily.

**Methocarbamol (Robaxin).** Robaxin is a monocarbamate ester of the guaiacol ether of glycerol. Its structure is shown in the following formula:



Methocarbamol
Robaxin
(3-*o*-methoxyphenoxy-2-hydroxypropyl-1-carbamate)

Robaxin is a white, crystalline powder which is soluble to about 4 per cent in water.

The carbamic acid ester group retards the metabolism of the glycerol side chain. This produces greater duration of action on the part of Robaxin, which appears to act as the intact molecule (Morgan *et al.*, 1957). Glycerol guaiacolate and its derivative, Robaxin, differ from other mephenesin-like drugs in possessing adequate water solubility to permit parenteral administration. Both drugs exhibit a lower hemolytic action than mephenesin (Truitt and Patterson, 1957).

Pharmacologic studies confirmed that Robaxin has a prolonged depressant action on the multisynaptic reflexes of the spinal cord and lower brain centers (Truitt and Little, 1957). This was demonstrated in animals by the finding of extended protection against strychnine, pentylenetetrazol, and electroshock convulsions.

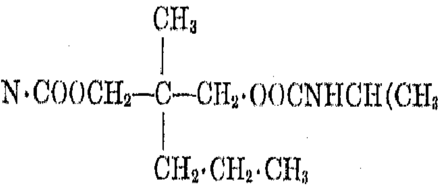
Robaxin is useful clinically for interrupting at the spinal synapses those reflexes which may originate from nerve irritation in strains, sprains, and other forms of trauma, and which reflexly cause painful muscle spasm. It is also useful in other diseases involving spinal hyperreflexia, such as cerebral palsy, multiple sclerosis, disc syndromes, cerebral accidents, and fibrositis. O'Doherty and Shields (1958) achieved excellent results with Robaxin in 14 of 17 cases of acute skeletal muscle spasm. Results were also good in acute fibromyositis and in patients with herniated lumbrosacral disk. Symptoms were promptly relieved on a dosage schedule of 4 gm. daily. They report further that the results of Robaxin therapy were not so impressive in the treatment of spasticity, rigidity, contractures, and incoordination. Other studies recorded indicate that Robaxin is a valuable addition to therapy in muscle spasm and severe flexor spasm accompanying disease of the spinal cord (Plumb, 1958).

Crandell and Whitcher (1960) used Robaxin successfully in conjunction with secobarbital and chlorpromazine in the control of the neuromuscular manifestations of tetanus. The sedative action of secobarbital and the muscle relaxant action of Robaxin appear to be potentiated by the use of chlorpromazine. It appears to be essentially free from side effects such as gastric discomfort, muscular weakness, and psychic disturbances.

Crookshank (1962) employed Robaxin intravenously and orally in 92 cases of back strain. In about ⅓ of the cases excellent results were achieved, and in more than half good results were obtained. He stated that in his experience the drug was safe and effective. Daily doses of 2 to 4 gm. evoke occasional drowsiness in a segment of the patients. Similar to meprobamate, sudden withdrawal from prolonged high dosage may precipitate convulsions.

Robaxin is available for intravenous use in doses containing 100 mg./ml. in aqueous polyethylene glycol-300. The dose is 10 ml. or 1 gm., diluted with 20 ml. of 5 per cent dextrose solution and administered 2 to 4 times daily.

**Carisoprodol (Soma).** Another interesting compound containing the carbamate ester linkage used as a skeletal muscle relaxant is Soma. Its structure is shown in the formula below:



$$H_2N\cdot COOCH_2-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_2\cdot CH_2\cdot CH_3}{C}}-CH_2\cdot OOCNHCH(CH_3)_2$$

Carisoprodol
Soma

(N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate)

Soma is a white, crystalline powder which is sparingly soluble in water.

*Pharmacologic properties.* The pharmacologic properties of Soma were studied by Berger *et al.* (1959). Soma was found to be a centrally acting skeletal muscle relaxant in a variety of laboratory animals. The relaxant action of Soma is estimated to be about 8 times greater than that evoked by mephenesin or meprobamate. Its effect is readily manifested in combating decerebrate rigidity, but it is only a weak antagonist of strychnine convulsive seizures. After the administration of Soma, the electroencephalographic (EEG) pattern showed high voltage and low frequency brain wave patterns and blockage of EEG activation. Soma differs from meprobamate in that it does not affect hippocampal seizures. The usual tests for analgesia indicated that Soma elicits weak analgesic activity. However the drug was capable of relieving joint pain induced by the injection of silver nitrate. The fate in the body (human studies) indicated that the biological disposition of Soma is similar to that of meprobamate, *i.e.*, most of the compound is excreted in the urine unchanged.

A series of chronic feeding studies in a variety of laboratory animals demonstrated the availability of Soma for trial in man.

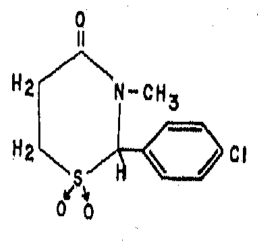
*Clinical use.* Although Soma is a comparatively new drug, its clinical use is already extensive. Soma relieves pain, spasm, and stiffness in many acute inflammatory, traumatic, or degenerative conditions affecting muscles and joints. The drug is valuable in patients with back injuries and disc syndromes. Kestler (1959) used the drug successfully in the relief of muscle spasm, pain and stiffness. Other clinical trials (Schlesinger, 1960 and Kuge, 1962) with Soma have demonstrated its effectiveness as a skeletal muscle relaxant. No serious side effects have been reported. Drowsiness may occur under a high dosage schedule. Tolerance has not been encountered.

The recommended dose of Soma is 350 mg. 3 times daily and at bedtime.

**Styramate (Sinaxar).** Among the carbamate acid esters used as muscle relaxants is the compound Sinaxar. Chemically Sinaxar is 2-phenyl-2-hydroxyethyl carbamate. The drug is recommended in skeletal muscle disorders similar to the other drugs previously discussed. It is reported to be well tolerated and does not produce drowsiness. Contraindications to Sinaxar have not been observed. It is claimed to exert its action over a 6-hour period after a single dose.

Sinaxar is available in 200-mg. tablets; 1 or 2 tablets are given 3 times daily.

**Chlormethanzanone (Trancopal).** Trancopal is a skeletal muscle relaxant with an entirely new type of chemical constitution as shown in the formula below:



Chlormethanzanone
Trancopal
(2-(4-chlorphenyl)-3-methyl-4-metathiazanone-1-dioxide)

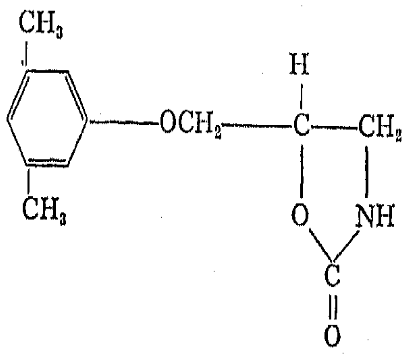
Trancopal is a white, crystalline powder which is sparingly soluble in water.

*Pharmacology.* The pharmacology of Trancopal was studied by Gesler and Surrey (1958). The skeletal muscle relaxant activity of Trancopal in laboratory animals was shown to be more potent than meprobamate. Trancopal protected animals against the convulsive seizures induced by electroshock, strychnine, and pentylenetetrazol. The drug showed selective blockade of polysynaptic spinal reflexes but showed no effect upon the monosynaptic knee-jerk reflex.

Trancopal evokes only a mild tranquilizing action. The drug evokes no relaxant effect on skeletal muscle directly or at the neuromuscular junction; its skeletal muscle relaxing action appears to be entirely central in origin. The drug has a low order of toxicity in laboratory animals; orally in mice the $LD_{50}$ is in the order of magnitude of 1680 mg./kg. Its margin of safety is approximately 13 when the $LD_{50}$ in mice is extrapolated and compared with the effective dose in man.

*Clinical use.* Extensive clinical trials with Trancopal have demonstrated its effectiveness in musculoskeletal conditions such as muscle spasm, low back pain, torticollis, and bursitis. It appears also to have value in the treatment of anxiety and tension states and dysmenorrhea. The principal side effects encountered with Trancopal are nausea and drowsiness. The occurrence of these effects, however, is in a small segment of patients. There appear to be no contraindications to the use of Trancopal. The usual dose of Trancopal is one 100-mg. tablet 3 or 4 times daily.

**Metaxalone (Skelaxin).** Skelaxin is a newer skeletal muscle relaxant remotely related chemically to Robaxin. Its structure is shown in the formula:



Metaxalone
Skelaxin
[5-(3,5-dimethylphenoxymethyl)-2-oxazolidinone]

Skelaxin is a white, crystalline powder that is very sparingly soluble in water. Skelaxin, like other skeletal muscle relaxants, blocks reflex spasm and spasticity by suppressing nerve impulses in polysynaptic pathways, primarily in the spinal cord and to a lesser degree at supraspinal levels. It exerts little or no effect upon monosynaptic pathways. It appears to be devoid of hypnotic or tranquilizing activity. The pharmacologic properties of Skelaxin were studied by Carroll *et al.* (1961).

*Clinical use.* Skelaxin is indicated in acute muscle spasm, strains and sprains, fractures and dislocations, and myalgia. Clinical results, although not numerous, indicate that the drug is effective in 85 per cent of the cases. Kurtzke and Gylfe (1962) found the drug an effective agent in reducing neurogenic spasticity. However, the untoward side effects were numerous and serious. For example, *liver toxicity* was found in 6 of 14 patients receiving Skelaxin, and a *reducing substance in the urine* of 7 of 14 patients receiving the drug was found. Nausea and gastrointestinal distress are the most frequently encountered side effects with Skelaxin. There have been indications of changes in the blood picture associated with the use of the drug. It appears to the authors that the slight superiority of Skelaxin over Robaxin, in conjunction with the side effects noted, does not justify its use unless the latter drug has failed.

Skelaxin is available in 400-mg. tablets. The daily recommended dose is 2 tablets 3 or 4 times daily.

**Chlorzoxazone (Paraflex).** Chemically Paraflex is 5-chlorobenzoxazolinone. It is recommended for use in the same conditions in which other skeletal muscle relaxants are used. Settel (1959) studied the drug in skeletal muscle spasm and related conditions. He achieved good results in 80 per cent of his patients and observed no adverse side effects.

Paraflex is administered in 250-mg tablets; 1 to 2 tablets are given 3 or 4 times daily.

## CHOREA

Chorea (Saint Vitus's dance) is a disease of the central nervous system. It is characterized by irregular and involuntary action of the muscles of the face and extremities. The disease may follow an acute infection such as rheumatic fever in young individuals and may disappear spontaneously (Sydenham's chorea or acute chorea). Lessof (1958) found from a study of 175 cases of Sydenham's chorea that there was evidence of rheumatic etiology in all but 11 cases. The disease may last for less than a week or more than a year. The mean duration is about 10 weeks. The disease may occur in older individuals as a definite hereditary entity (Huntington's chorea). It is marked by irregular muscular movements, disturbances of speech, and dementia.

**The use of drugs in chorea.** There is no specific therapy for chorea. Treatment is designed to control the muscular movements and to protect the patient from injury resulting therefrom. Phenobarbital is given, 32 mg. 3 times a day. Opiates should be avoided. If the patient's condition is not controlled by phenobarbital, 2 to 10 ml. of paraldehyde may be administered in oil, either to supplement or in place of the barbiturate therapy (Schwentker, 1955). ACTH has been recommended, but its value in chorea has not been established.

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# 28

# *Central Nervous System Depressants. Miscellaneous Hypnotics*

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In addition to the various derivatives of barbituric acid discussed previously, there are several other hypnotic drugs in use in medical practice today. Among these drugs are chloral hydrate, paraldehyde, carbromal, Valmid, and other newer hypnotics. Indeed, each of these compounds has its special use as a hypnotic and general sedative to the central nervous system. Their special uses will be discussed in this chapter.

## Chloral Hydrate, U.S.P.

Chloral hydrate, $CCl_3CH(OH)_2$, was first synthesized by Liebig in 1832. It is the first synthetic hypnotic. The hypnotic properties of chloral hydrate were not observed, however, until 1869.

**Chemical and physical properties.** When acetaldehyde is treated with chlorine, trichloroacetaldehyde, $CCl_3 \cdot COH$ is formed. This is called chloral. It is a heavy, acrid oil. Chloral combines energetically with water and forms its monohydrate, which is designated as *chloral hydrate.* The hydrate occurs as colorless, transparent, or white crystals. It has a characteristic penetrating odor and a slightly bitter, caustic taste. It is soluble in 0.25 part of water and also freely soluble in alcohol, glycerin, and oils.

**Absorption, fate, and excretion.** Chloral hydrate is readily absorbed from the gastrointestinal tract. On the gastric mucosa the compound produces some irritation. For many years it was believed that chloral hydrate was decomposed into chloroform in the blood and tissues. When the compound is treated with alkali hydroxides, it yields chloroform and alkali formate.

The evidence is convincing that this does not occur in the tissues. In the body chloral hydrate is for the most part reduced to trichloroethanol, $CCl_3 \cdot CH_2 \cdot OH$, which is conjugated with glycuronic acid to form *urochloralic acid*. This conjugate is excreted in the urine. This substance reduces alkaline copper solutions (Fehling's and Benedict's), and hence its presence in the urine might be mistaken for glucose.

Butler (1948) studied the capacity of various tissues to reduce chloral hydrate to trichloroethanol and to oxidize it to trichloroacetic acid. All of the many tissues studied of the dog and rat were capable of reducing chloral hydrate. Oxidation of chloral hydrate to trichloroacetic acid, however, was demonstrated only by kidney and liver of both species.

Owens and Marshall (1955) gave chloral hydrate to individuals at a fixed dosage level. They found the fraction oxidized to trichloroacetic acid varied in the same individual on different days. In some persons nearly the entire amount of chloral hydrate given could be accounted for by the trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid excreted in the urine. Others excreted only a small fraction of the dose as these products. Trichloroethanol glucuronide was found to be concentrated in and secreted by the bile.

**Pharmacologic responses.** Chloral hydrate in therapeutic doses serves as an excellent hypnotic. From 20 to 30 minutes after ingestion a feeling of drowsiness is produced, and sleep soon ensues. The sleep lasts for 6 to 8 hours, and as a rule lassitude is not present after awakening.

When used in hypnotic doses, the central nervous system depression is confined to the cerebral hemispheres, and the vital medullary centers are not affected. The patterns of other functions, such as blood pressure and pulse, do not differ from those shown in normal sleep.

Like other depressants of the central nervous system, massive doses of chloral hydrate produce deep narcosis and depression of respiration. It can produce anesthesia, but as an anesthetic its margin of safety is too small.

Tolerance and habituation may occur if chloral hydrate is given repetitiously. There is no evidence of withdrawal symptoms. The tolerance is said to occur from the increased capacity of the liver to conjugate chloral and its alcohol formed by reduction as glycuronate and sulfonate. Like other halogenated derivatives of aliphatic compounds, excessive use of chloral hydrate might produce hepatic damage. When this occurs, tolerance to the drug disappears, and the larger dosage might cause severe central nervous system depression.

**Toxicology.** The margin of safety with chloral hydrate is fairly large. Deaths have resulted from the administration of 3 to 30 gm. of the drug. Death is due to the depression of the respiratory centers. Caffeine-sodium benzoate injection and oxygen inhalation are useful in combating the intoxication. Amphetamine is valuable to support the circulation.

It was believed that chloral hydrate and alcohol together were much more potent than the sum of the effects of the two depressants. The mixture of chloral hydrate and distilled alcoholic beverages is known as a "Mickey Finn" or "knockout drops." Alcohol does unite with chloral to form an alcoholate. Adams (1943) administered the hydrate and alcoholate of chloral, respectively, to 500 rats. He found no significant difference in their toxicities.

### Therapeutic uses and dosage.

The principal therapeutic use of chloral hydrate is to produce sedation. It is employed as a sedative in hysteria and hyperexcitability and as a hypnotic in insomnia caused by anixety. It has no capacity to obtund pain if it does not produce sleep.

Chloral hydrate is prescribed in solution, generally with a flavoring syrup such as ginger or cherry, or in capsules. Its official dose is 0.6 gm.

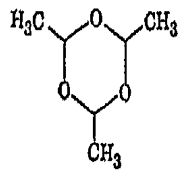
### Pentaerythritol Chloral (Perichlor).

A compound of chloral and pentaerythritol has been recently made available as a hypnotic. Chemically Perichlor is tetrachloralpentaerythritol, which contains 81.3 per cent of chloral in a hemiacetal structure. Chloral hydrate contains 89.1 per cent of chloral. Perichlor occurs as a colorless mass which may be ground to a white powder, which is slowly soluble in water. Perichlor does not emit the characteristic pungent odor of chloral hydrate.

Perichlor undergoes hydrolysis in artificial gastric juice to the extent of 50 per cent in 1 hour. The products of hydrolysis are chloral and pentaerythritol. The action of Perichlor appears to be closely similar to that of chloral hydrate. Gatski (1955) found a suitable hypnotic dose of the agent to be between 0.5 and 1 gm. He found that a longer period of sleep was elicited by Perichlor than by chloral hydrate. The hypnotic action of Perichlor, similar to that of chloral hydrate, is rapid in onset. Perichlor was found useful for daytime sedation in doses of 0.3 gm. every 4 to 6 hours. The principal advantages of Perichlor appear to be a better degree of gastric tolerance and achievement of sedation with a lower dosage schedule. Perichlor enjoys a rather wide margin of safety between its hypnotic and toxic doses.

### Paraldehyde, U.S.P.

Paraldehyde is a trimer of acetic aldehyde obtained by treating the latter with concentrated sulfuric acid. Its structure is shown in the formula below:



Paraldehyde, U.S.P.

Paraldehyde is a clear, colorless liquid. It has a strong characteristic odor and elicits a pungent disagreeable taste. One ml. of paraldehyde dissolves in 8 ml. of water; it is readily soluble in alcohol.

**Pharmacologic response.** Within 30 minutes after administration in therapeutic doses, paraldehyde produces a feeling of drowsiness and desire for sleep. The depression is mainly in the sensory areas of the cerebral cortex. In therapeutic doses the drug does not affect the medullary centers. Generally the sleep produced by paraldehyde leaves the subject without much feeling of drowsiness in the morning. The hypnotic dose of paraldehyde is 4 to 8 ml. When this dose is increased, profound sleep and analgesia can be produced.

**Fate, excretion, and toxicity.** Paraldehyde shows a variety of metabolic patterns, depending upon the species to which it is given. In the rat it is almost entirely excreted, unchanged, in the exhaled air. In man most of the drug is detoxified by the liver. This fate obtains also in the dog. If the liver of the dog is first poisoned with chloroform, its capacity to detoxify paraldehyde is diminished. In these animals normal doses produce long periods of narcosis.

Levine *et al.* (1940) showed that from 11 to 28 per cent of the paraldehyde administered to dogs was excreted by the lungs. Only a very small fraction was excreted by the kidneys. Approximately 75 per cent of the drug was destroyed by the liver. In normal hypnotic doses in the dog, Bodansky *et al.* (1941) found about 50 mg. per cent of paraldehyde in the blood.

**Therapeutic uses.** The principal use of paraldehyde is as a *sedative* and *hypnotic*. It is used in producing sedation in delirium tremens and in bromide psychoses. As a hypnotic in insomnia it has limitations because it produces gastric irritation and has a disagreeable taste. However, when one suspects that a patient may become a habitué to a hypnotic drug such as pentobarbital, paraldehyde may be advantageously employed. The individual is generally pleased to discontinue its use.

### Chlorobutanol, U.S.P.

Chlorobutanol was introduced under the name of **Chloretone.** Chemically it is trichlorotertiary butyl alcohol, as shown by the formula:

$$Cl_3C \cdot C(CH_3)_2 \cdot OH$$

Chlorobutanol occurs as colorless or white crystals. It possesses a pleasant mint-like odor and elicits a bitter, camphoraceous taste. One part of the compound dissolves in 125 ml. of water. It is readily soluble in alcohol.

**Pharmacologic response.** This compound possesses interesting pharmacologic properties. It is a depressant to the central nervous system and serves as a hypnotic. In larger doses orally or by vein it is a useful anesthetic in laboratory animals. The compound is an antiseptic, and in this capacity it is about 15 times stronger than boric acid. As a bacteriostatic agent chlorobutanol has been used for years as a preservative in a large number of preparations intended for parenteral use. In addition, the drug exhibits local anesthetic action on mucous membranes.

**Absorption and fate.** Chlorobutanol is readily absorbed from the gastrointestinal tract. It is decomposed in the body, presumably by the liver.

**Therapeutic uses.** The principal therapeutic use of chlorobutanol is in the treatment of nausea and vomiting, especially produced by seasickness. The sedative action of the drug tranquilizes the individual. The local anesthetic action desensitizes the mucous membranes of the stomach and diminishes nausea. The mint-like odor of the drug is desirable, and in many individuals the drug acts as a carminative. The dose is 0.6 gm. in capsules.

Locally, chlorobutanol is used as an inhalant. For this purpose a 1 per cent solution in light liquid petrolatum is employed. Camphor, menthol, and oil of cinnamon are the other ingredients.

### Carbromal, N.F.

This compound is sold under the name of **Adalin.** It has been used for years as a sedative and hypnotic. Chemically it is bromodiethyl acetylurea, as shown by the formula:

$$(C_2H_5)_2CBrCONHCONH_2$$

Carbromal is a white, odorless, crystalline powder. It is soluble in 3000 parts of water and 18 parts of alcohol.

**Pharmacologic response.** Carbromal is a dependable sedative. It allays excitement and anxiety and tends to restore a state of quiet and tranquility. It is not a powerful hypnotic, and its action is less prompt than many of the barbiturates.

In therapeutic doses carbromal is reported not to affect the heart, circulation, or respiration.

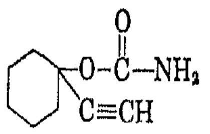
The sleep produced by carbromal appears to be physiologic in character, quite devoid of unpleasant after-effects. There is little morning drowsiness after sleep induced by carbromal. Indeed, considering the wide use of the barbiturates today, it is strange that this drug is not more extensively used, although in recent years interest is reawakening in the use of carbromal. It may be used concurrently with one of the barbiturates when its potency as a sedative appears to be too mild.

**Therapeutic uses.** The principal use of carbromal is as a sedative and mild hypnotic. For this purpose it has found a use in anxiety states, chorea, mental disorders with excitement, and insomnia resulting from various causes. It has no power to obtund pain. The dosage of carbromal is large; as a hypnotic it is given in 0.6- to 1.3-gm. capsules. It is most effective if followed by warm milk or diluted tea. As a sedative 0.3 to 0.6 gm. administered 3 to 4 times daily is sufficient.

## NEWER HYPNOTICS

### Ethinamate N.F. (Valmid).

Valmid is one of the newer nonbarbiturate hypnotics containing the acetylenic triple bond, as shown in the following formula:



Ethinamate N.F.
Valmid
(1-ethynylcyclohexyl carbamate)

The structure shows a carbamic acid ester of cyclohexyl alcohol with the acetylenic group attached to the same carbon atom as that of the ester linkage. Valmid is a white, crystalline powder which is insoluble in water.

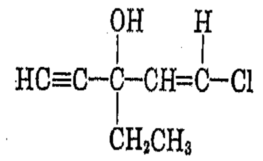
**Pharmacologic action and therapeutic use.** Ethinamate was studied pharmacologically by Gruber *et al.* (1954) and observed to produce a single response, namely, mild sedation and hypnosis. The compound has a low toxicity on various laboratory animals. Organs such as the brain, liver, kidney, and bone marrow were not injured by the prolonged ingestion of ethinamate. Swanson *et al.* (1956) observed that the repetitious injection of ethinamate intravenously in the dog caused a gradual fall in blood pressure, a bradycardia, slowed respiratory rate, and ultimate death by respiratory failure. The respiratory failure was combated by picrotoxin or artificial respiration. The fate of ethinamate in the body appears not yet to be established. Only small fractions of a large total dose were recoverable from the urine of dogs. In animals whose livers were damaged with carbon tetrachloride, the hypnotic action of ethinamate was not intensified, indicating that the liver is not the site of metabolism of the compound.

Clinically, the principal effect of ethinamate is that of evoking sleep. The onset of action is prompt (20 to 30 minutes), and the duration of action is short, generally about 4 hours. From the studies of Gruber *et al.* (1954) the sedative effect of a dose of 500 mg. of ethinamate was shown to be comparable to that produced by 100 mg. of secobarbital sodium, but of shorter duration. Of special interest is the fact that ethinamate is well tolerated by patients with hepatic disease who do not tolerate well the short-acting barbiturates. Gruber (1956) reported that in Germany 39 individuals have attempted suicide with ethinamate. There were 2 deaths, and 1 of these was associated with the ingestion of other sedatives in addition to ethinamate. It is clear that serious central nervous system depression similar to that elicited by large doses of the barbiturates can be evoked by ethinamate.

Lasagna (1957) states, "Our experience with one of ethinamate given at bedtime to hospitalized patients has been very satisfactory to date." Usually Valmid has to be given in 1-gm. doses in order to achieve therapeutic effectiveness in the majority of patients. This drug appears to be a valuable sedative, and time alone will assess its ultimate place in the group of hypnotic drugs.

### Ethchlorovynol, N.F. (Placidyl).

Ethchlorovynol is another hypnotic containing the triple bond acetylenic group as shown in the formula:



$$\mathrm{HC{\equiv}C{-}\overset{OH}{\underset{CH_2CH_3}{C}}{-}CH{=}\overset{H}{C}{-}Cl}$$

Ethchlorovynol, N.F.
Placidyl
(β-chlorovinyl ethyl ethynyl carbinol)

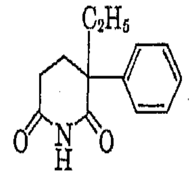
Ethchlorovynol occurs as a liquid which boils at 73°C. Its specific gravity is 1.07. It is insoluble in water. Ethchlorovynol emits a penetrating camphoraceous odor.

**Pharmacologic action and therapeutic use.** Margolin *et al.* (1951) established the sedative and anticonvulsive actions of a number of the higher acetylenic carbinols. It was shown by P'an *et al.* (1953) that the activity of these compounds was increased by halogenation. Ethchlorovynol offered promise of therapeutic usefulness in the series of compounds studied. The primary pharmacologic effect of ethchlorovynol is to induce sleep. The compound has a low order of toxicity and appears to be metabolized in the body. Impaired liver function does not accentuate its effect. No tolerance was developed when ethchlorovynol was administered repeatedly to dogs, and there was no evidence of chronic toxicity to the important viscera. Rhesus monkeys fell asleep within 30 to 60 minutes after the administration of 125 to 150 mg. of ethchlorovynol.

Ethchlorovynol has had wide clinical trial in a variety of patients. Paul (1956) found it useful in inducing sleep in patients with chronic diseases. Lasagna (1957) observed similar satisfactory results with ethchlorovynol, using 1 gm. at bedtime as a hypnotic in hospitalized patients. He found a dose of 300 mg. adequate for most patients. Rosenloff and Grisson (1957) compared the hypnotic response evoked by 50 mg. of secobarbital sodium with that produced by 500 mg. of ethchlorovynol. A significantly greater number obtained satisfactory hypnosis with ethchlorovynol than with secobarbital. It occurs to the authors that a more valid comparison would have been achieved by the use of a 100-mg. dose of secobarbital. Other reports indicate the onset of hypnotic action from 500 mg. (capsules) of ethchlorovynol to be between 15 and 30 minutes and the duration about 5 hours. In some patients with insomnia, ethchlorovynol must be given in doses of 1 gm. to achieve successful hypnotic action.

### Glutethimide, N.F. (Doriden).

Glutethimide is a completely new structure for a hypnotic drug, shown in the formula:



Glutethimide, N.F.
Doriden
(2-ethyl-2-phenyl-glutarimide)

Glutethimide is a white, crystalline powder which is nearly tasteless. It is relatively insoluble in water but easily soluble in alcohol. Chemically, the molecule differs from that of phenobarbital in that the $(CH_2 \cdot CH_2)$ group replaces one of the $(CO \cdot NH)$ groups in the pyrimidine nucleus.

**Pharmacologic action and therapeutic use.** Pharmacologic studies with glutethimide in various laboratory animals showed that its primary action is that of inducing sedation and sleep. The compound exhibits a low acute toxicity, and chronic feeding in dogs and rats produced no visceral damage or blood dyscrasias. No cumulative effect was observed in a period of 6 months, and no withdrawal syndrome was precipitated in dogs upon abrupt discontinuance of the drug. Schreiner *et al.* (1958) observed that glutethimide, after absorption, is excreted in the bile to the extent of 85 per cent of the ingested dose. It is presumably available for reabsorption from the intestine and then excreted in the urine as a conjugate or metabolite.

Several clinical reports indicate that glutethimide in 250- to 500-mg. doses will induce sleep in normal people and in chronically ill patients. There appear to be few untoward side effects and a minimum of "hang-over" in the morning. Occasional gastrointestinal disturbance and skin rash have been reported. Others have reported occasional dizziness, xerostomia, confusion, ataxia, excitement, and grogginess after the use of glutethimide (Matlin, 1956; Weston, 1956). Deep coma was produced in 1 patient who ingested 10 gm. of glutethimide. The syndrome was similar to acute barbiturate intoxication (Blakey *et al.*, 1956).

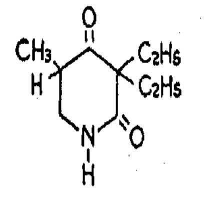
Other poisonings with glutethimide were reported by Schreiner *et al.* (1958) in 5 women and 1 man. Deep coma, areflexia, severe hypotension, and hypoventilation prevailed after the ingestion of 7 to 12 gm. of glutethimide. One death occurred after 10 gm. of the drug, but the case was complicated by the ingestion of alcohol with the hypnotic. With the use of the analeptic Megimide and hemodialysis, recovery was achieved in 5 of the 6 patients. The blood level of glutethimide in severe intoxication varied from 1 to 3 mg. per cent.

Fastier (1958) compared glutethimide with pentobarbital and placebos in student volunteers. In one trial 500 mg. of glutethimide was not more effective than a placebo, whereas 200 mg. of pentobarbital evoked a powerful hypnotic response. In another test 700 mg. of glutethimide compared favorably with 150 mg. of pentobarbital in onset and duration of sleep and after effects. The only side effect noted with glutethimide was xerostomia.

Glutethimide is recommended also for daytime sedation; 250 mg. is the approximate equivalent of 30 mg. of phenobarbital. For hypnotic purposes glutethimide in a dose of 500 mg. may be expected to act within 15 to 30 minutes. Its duration of action may extend for 4 to 8 hours.

## Methyprylon, N.F. (Noludar).

Methylprylon is a hypnotic compound containing a piperidine nucleus as shown in the formula:



Methyprylon, N.F.
Noludar
(3,3-diethyl-5-methyl-2,4-piperidinedione)

Methyprylon occurs as colorless crystals which are water soluble. The solution is slightly acid.

**Pharmacologic action and therapeutic use.** Experiments in laboratory animals revealed that the primary action of methyprylon is that of sedation and hypnosis. The therapeutic index of the drug is high. When administered orally to mice, the ratio between the hypnotic dose and the fatal dose was more favorable than that of phenobarbital under the same conditions. The prolonged administration of methyprylon did not produce visceral changes or blood dyscrasias in laboratory animals.

In a large series of cases Brandman *et al.* (1955) found that methyprylon served as a satisfactory hypnotic. Sleep was induced within 30 minutes and the average duration was 7 hours. Undesirable side effects such as hang-over or morning drowsiness, vertigo, and nausea occurred in 1.3 per cent of the patients. Repetitious 250-mg. doses nightly for 4 weeks elicited no toxic side effects or changes in the blood picture. These investigators observed that 50 mg. of methyprylon 3 times a day induced sedation comparable to that of 15 mg. of phenobarbital 3 times daily.

Loughlin *et al.* (1955) observed that methyprylon provided adequate hypnosis in 94 per cent of 88 cases. No toxic manifestations were revealed by liver and kidney function tests in this series of patients. Side effects such as nausea, vomiting, constipation, drowsiness, excitation, vertigo, headache, pruritus, skin rash, and diarrhea have been reported following the use of methyprylon. The incidence of these effects, however, seems low (Lasagna, 1957).

Pellegrino and Henderson (1957) reported a case of the ingestion of 3.4 gm. of methyprylon in attempted suicide. The patient was deeply comatose 2 hours after the ingestion of the drug. After gastric lavage and supportive treatment, the patient became completely asymptomatic in 12 hours.

The recommended dose of methyprylon as a hypnotic is 200 to 400 mg. The daytime sedation dose is 50 to 100 mg. 3 times a day.

## Methylparafynol (Dormision).

The use of this compound as a hypnotic has diminished. For a discussion of the drug, see the 5th edition, page 682.

With the introduction of several new nonbarbiturate hypnotics within the past several years, one is inclined to evaluate the contribution they have made in the management of insomnia. Each appears to be less dependable than the barbiturates and fraught with a greater incidence of side effects. Acute intoxication appears possible with each of these drugs, which require larger dosage to produce the acute depression syndrome than with the currently used barbiturates. Their effective hypnotic doses are larger than those of the barbiturates. It is true that these compounds offer the physician an alternate sedative for patients who become barbiturate-tolerant or who are adversely affected by the barbiturates. It does appear to the authors, however, that the barbiturates remain the drugs of choice in the management of insomnia. Lasagna (1957) states, "The evidence to date provides no compelling reason for believing that any of the newer hypnotics differ qualitatively from the barbiturates in their desirable or undesirable attributes."

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# 29

# *Central Nervous System Depressants. The Analgesics and Antipyretics*

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Man has ransacked this entire globe to obtain drugs with which he might achieve a surcease from pain. In "Paradise Lost" Milton declared, "Pain is perfect misery, the worst of evils; and excessive, overturns all patience." Physiologically, pain is a *specific sensory experience which is mediated through nerve structures which are separate from those which mediate other sensations such as touch, pressure, heat, and cold.* Pain is recognized as a warning signal of danger to the organism. The clinical control of severe pain is considered important in allaying emotional distress. Besides, intractable pain can produce damage to such organs as the heart and kidneys.

In the consideration of the treatment of pain with drugs, the following information is basic.

1. Intensity of pain is not proportional to the extent of severity of tissue damage. Beecher (1946) questioned 215 recently wounded men in the combat zone during World War II. The wounds were severe and represented a wide variety of tissue damage. All were rational. Only 24 per cent reported "bad pain." The others expressed only moderate, slight, or no pain.
2. The measurements of the threshold of perception to pain stimuli by various workers with different technics, page 272, have shown that *all persons in a healthy state have about the same capacity for perceiving pain.* Little daily or periodic variation was observed in the same individual. Although the threshold to the specific nerve stimulus, "pain," is essentially the same for various individuals, the anguish or displeasure provoked by the same pain stimulus in different individuals varies tremendously. The degree of "alarm," the emotional trauma produced by the pain, is an essential segment of the pain syndrome which must be treated.
3. It has been established that sensory nerve fibers, of the large "A" myelinated type, conduct impulses at speeds up to 100 meters a second. The "B" small myelinated fibers conduct impulses at speeds of 3 to 14 meters a second, and the "C" unmyelinated fibers conduct at a speed of less than 2 meters a second.

   Bright, piercing, poignant pain is carried by "A" type fibers. Burning pain is conducted by smaller fibers of the "B" type. Aching pain in muscles and joints appears to be conducted by "B" and "C" type fibers. Generally speaking, pain may be conveniently classified into *cutaneous* or *integumental pain* and *visceral pain.* The former is characterized by a "bright" quality. It is conducted rapidly over "A" type fibers. It may excite the individual, prepare him for flight or combat. Visceral pain, on the other hand, is characterized by a deeper burning, aching quality. It is depressing, produces anxiety, and frequently anorexia and vomiting. It appears to be conducted slowly over unmyelinated "C" fibers. These different pain qualities respond differently to different drugs.

   Quantitatively, the degrees of integumental pain have been measured by the Wolff-Hardy-Goodell technic, page 272. It was demonstrated that there were approximately 22 increments of intensity between the threshold to pain and the maximal pain intensity. Two of such degrees or pain increments have been designated as a *pain unit* or a *"dol."*

The work of Starzl and Magoun (1951) has made it necessary to consider the *ascending reticular system* in our concepts of the awareness of pain. Magoun has shown that these nerve cells, which lie in the brain stem, interspersed between the main sensory and motor pathways, are concerned with the arousal from sleep. If the reticular formation is stimulated while an animal shows a sleep pattern electroencephalogram, the pattern changes to the dys-synchrony of the waking state. Destruction of the area produces a persistent stuporous state from which only strong sensory stimuli will cause only a brief arousal. However, if the main sensory pathways are destroyed at the upper level of the brain stem, peripheral stimuli will still arouse a sleeping animal with an intact reticular formation. These experiments indicate that the main sensory pathways send collaterals into the reticular formation, and further, that these neurons are involved in the perception of pain as much as the main sensory pathways to the cortex. It appears that the awareness of pain is dependent upon the final pattern of the noxious stimulus which reaches the sensorium, and further, that the stimulus is subject to modification at all levels from the point of entry to the sensorium itself.

The general anesthetics obliterate pain by producing a hiatus in consciousness. Morphine obtunds pain by its action on the cerebral cortex, increasing the pain threshold. The analgesics to be discussed in this chapter, often called the "coal tar analgesics," are useful in allaying pain. In the production of analgesia by the drugs of this series, such as aspirin, acetanilid and acetophenetidin, there is no interference with mental alacrity. Moreover, the drugs do not affect the motor cortex nor reduce activity in skeletal muscle.

The analgesics of this series are not effective in the relief of deep-seated visceral pain. They are not efficacious in affording relief from excruciating, sharp, and intense pain. These analgesics are most valuable in the relief of arthralgias, myalgias, neuralgias, cephalalgias, and integumental pain in general.

Most of the analgesics of the series serve also as *antipyretics, i.e.*, they cause a reduction in temperature when administered to fevered individuals. They appear to exert little effect on bodily heat production. In the main these agents cause a reduction in body temperature of a fevered individual by increasing heat elimination. According to Barbour and Aydelotte (1933), the antipyretic drugs accomplish this result by drawing water from the tissues into the circulation, thus increasing the fluid volume which is passing through the heat-radiating system of the body.

The heat-regulating system located in the hypothalamus is the likely site for the mediation of these changes. This center controls body temperature through the transmission of sympathetic influences to cutaneous vessels, sweat glands, and pilomotor muscles. Barbour and Aydelotte showed that foreign bodies applied to this area of the brain caused a rise in body temperature. On the other hand, the local application of the antipyretic drugs caused a fall in body temperature. It is believed that the antipyretic drugs modify hypothalamic function in such a way as to reduce body temperature in hyperpyrexic individuals.

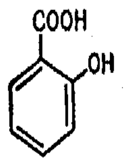
Because of the action of these analgesics, serving also as antipyretics, it is believed that their analgesic response is elicited from action in the brain at subcortical levels. *They appear to interfere with pain impulses carried over the lateral spinothalamic tract.* It is unlikely that they block the synapse in the cord. Their action as antipyretics in the region of the thalamus suggests that they raise the threshold of pain stimuli relayed from the thalamus to the cerebral cortex. It is also probable that the relief of integumental pain by the coal tar analgesics involves a peripheral component. Aspirin and the salicylates promote the removal of fluid from inflamed areas, thus diminishing the pressure on nerve endings and thereby relieving pain. Winder (1959) suggests that the central analgesic effect of such drugs as aspirin and aminopyrine is effectively enhanced by a peripheral component. This peripheral effect is an *antipreinflammatory* action related to the nonsteroidal antirheumatic action. The over-all analgesic effect according to Winder is the result of the central and peripheral actions.

With the relief of pain mediated by morphine the tranquilizing of the patient and suppression of the alarm reaction often endures longer than the increase of the threshold to pain. With this type of analgesia a second noxious stimulus reaching the sensorium is acutely recognized. With analgesia produced by the coal tar analgesics, additional noxious stimuli are not perceived because of the blockade of the pain pathway below the sensorium.

## Salicylic Acid, U.S.P., and Its Derivatives

Salicylic acid was obtained first from salicin, a glucoside found in the willow and poplar barks, by Piria in 1838. It is found also in nature as its methyl ester in oil of wintergreen. Salicylic acid is now prepared synthetically from phenol.

**Chemical and physical properties of salicylic acid.** Salicylic acid is orthohydroxybenzoic acid as shown by the accompanying formula.



Salicylic Acid, U.S.P.

As an analgesic, only the orthohydroxybenzoic acid has been found useful. The meta and parahydroxybenzoic acids are of no value in the treatment of rheumatic fever and other conditions where salicylic acid is a dependable drug.

The alkylation of the hydrogen atom of the hydroxyl group and the introduction of other groups on the benzene nucleus have not conferred advantages on salicylic acid as a therapeutic agent.

Salicylic acid occurs as white crystals, usually fine needles, or as a white, fluffy, crystalline powder. It has a sweetish and afterward acrid taste. It is soluble in 460 ml. of water and 3 ml. of alcohol. The aqueous solutions of salicylic acid are strongly acid to litmus, pH 2.4.

Salicylic acid is generally employed internally in the form of its sodium salt or one of its esters such as acetylsalicylic acid or aspirin. Locally it is used as the free acid to remove horny layers of skin in epidermophytosis and similar conditions. The free acid has antiseptic properties approximately equal to those of phenol.

**Response of the central nervous system to salicylates.** When the salicylates are administered to unfevered individuals, their *principal action is to serve as an analgesic.* They do not reduce normal body temperature. The analgesic action is manifested experimentally in humans by a decreased sensitivity of the skin to painful stimuli. The analgesia is of little value in visceral pain. It is likely mediated through its action in the thalamus, increasing the threshold to pain stimuli relayed to the sensory cortex.

In hyperpyrexic individuals salicylates reduce the fever. The mechanism of action of the antipyresis has been the subject for study by many investigators. Barbour and Aydelotte (1933) showed that the salicylates and related drugs produced an action on the heat centers. When the antipyretics of the salicylic acid series are given, the heat production in the individual is diminished only slightly. Peripheral vasodilatation is produced, and heat loss is increased by radiation. Sweating occurs, and heat loss is mediated through this mechanism. Barbour has further emphasized the role of alterations in water balance in fever and its reduction. In fever, water is shifted from the blood to the liver, subcutaneous tissue, and skeletal muscle. He suggests that in fever reduction produced by the salicylates, a reversal of this phenomenon is initiated by the drug. Indeed the evidence is quite clear that in the fevered individual increased heat loss is responsible for most of the fever reduction. Decreased heat production plays a comparatively minor role.

The usual therapeutic doses of the salicylates do not affect other functions of the central nervous system. In massive doses the drug first stimulates and then depresses the respiratory centers. Death is generally due to respiratory arrest.

Various investigations have indicated that acidosis produced by massive doses of salicylates is the result of renal adjustment to the respiratory changes produced by the drug. In cases of salicylate poisoning the respiration is deep and rapid, and the rate may be as high as 38 per minute. The hyperpnea may resemble the Kussmaul type characteristic of diabetic acidosis.

Experimental studies on dogs have shown that the intravenous injection of large doses of salicylates causes definite hyperventilation. Graham and Parker (1948) observed that all patients show hyperventilation, and some exhibit severe dyspnea when the plasma levels of salicylate are above 35 mg. per cent. Severe dyspnea occurs in most patients when the plasma level reaches 50 mg. per cent.

**Salicylates on the heart, blood, and blood vessels.** The ordinary therapeutic doses of the salicylates produce no significant effect on the heart or the blood vessels. Large doses of salicylates relax the smooth musculature of the blood vessels and produce vasodilatation. Massive doses which depress the respiratory centers may also depress the vasomotor center. Perfusion experiments with the salicylates show that the heart is not deleteriously affected by concentrations of salicylates observed in the blood of man even after massive doses.

One of the positive effects of salicylates is on the sedimentation rate. This is markedly reduced by salicylates, especially if it has been previously elevated by disease. The effect is produced *in vitro* and also is manifest in the shed blood of individuals who have ingested salicylates. The fibrinogen in the plasma is reduced by the administration of salicylates. The concentration required for the effect of salicylate *in vitro* is approximately 100 mg. per cent. This level is never achieved by the administration of salicylates. It has therefore been suggested that salicylates might also diminish the production of fibrinogen by the liver. The level of fibrinogen may be reduced as much as 50 per cent, and the reduction appears to be a function of the dose of the salicylate. Large doses of salicylates increase the clotting time of blood. Plasma prothrombin is decreased and the prothrombin time is prolonged.

**The salicylates on metabolism.** Salicylates diminish the renal threshold to uric acid and increase the excretion of urates. The excretion of uric acid may be increased from 30 to 100 per cent by the administration of salicylates. Endogenous and exogenous uric acid excretion is stimulated by salicylates, and the blood-uric acid level may drop significantly when salicylates are given. Other nitrogenous constituents of the blood are not significantly altered by salicylates. It appears therefore that the salicylates exert a specificity on the renal threshold of uric acid. This action of the salicylates is an important factor of their beneficial action in gout. Large doses of salicylates have been shown to cause a depletion of liver glycogen.

Reid (1960) produced evidence to show that salicylate is a primary metabolic stimulant with, possibly, pulmonary ventilation increasing to meet a peripheral demand for more oxygen. This is associated with a relative fall in carbon dioxide production, increased protein catabolism, and resultant respiratory alkalosis. This is a new type of respiratory alkalosis. It is possible that the antirheumatic action of salicylate is related to its metabolic stimulating action. This is an interesting and refreshing contribution to our knowledge of salicylate action.

Reid *et al.* (1957) observed that intensive salicylate therapy abolished the glycosuria and returned the fasting blood sugar level to normal in 7 mild to moderately severe diabetics. The dosage schedule provided serum salicylate levels of about 40 mg. per cent. The usual symptoms of salicylism prevailed but were tolerated quite well by the patients. Of special interest is the fact that the metabolic rate of the patients increased significantly in response to the therapy.

Reid and Lightbody (1959) confirmed this observation and established the insulin equivalence of salicylate. It was observed that as many as 48 units of insulin daily could be replaced by salicylates. The dosage level of aspirin was from 0.7 to 1.5 gm. 5 times daily, thus establishing serum salicylate levels of 30 to 50 mg. per cent. The usual untoward effects of massive salicylate therapy such as tinnitus, deafness, nausea, and anorexia were encountered in segments of their patients. It is of interest that Manchester *et al.* (1958) observed that salicylate, like insulin, increased the glucose uptake of the diaphragm of the rat.

Packer *et al.* (1959) showed that salicylate and acetylsalicylate increased respiration in rat heart sarcosomes. Many of the analogs of salicylic acid were inactive. The extent of stimulation of respiration evoked by salicylates in rat heart mitochondria, oxidizing $\alpha$-ketoglutarate in a phosphate-acceptor deficient system, was used as a criterion to indicate the uncoupling of oxidative phosphorylation. That this capacity of salicylate to uncouple oxidation from phosphorylation is likely not associated with the antirheumatic action is shown by the fact that gentisic and resorcylic acids did not serve as uncouplers of oxidative phosphorylation. Evidence appears to be emerging from many sources to indicate that salicylates exert a profound influence on tissue metabolism.

Reid (1960) observed that aspirin increased the gaseous metabolism and lowered the serum cholesterol level of myxedematous patients. Further, it was observed that full therapeutic doses of 4 to 6 gm. daily decreased the hypercholesterolemia in various types of euthyroid subjects, but not without side effects. In a series of patients with coronary insufficiency and in diabetics, aspirin lowered the serum cholesterol level about 25 per cent in 28 per cent of the patients studied. Reid found aspirin to be as efficient in reducing hypercholesterolemia as triiodothyronine. Again, the side effects of salicylism were found disturbing to the patients.

These findings were confirmed by Eidlitz (1960). He found aspirin effective, in doses of 1.5 gm. daily, in reducing hypercholesterolemia in patients for a period of 2 weeks. In some patients, however, the serum cholesterol level increased during therapy.

It appears that this action of aspirin stems from the stimulating action that the drug evokes on metabolism. Implicit in this statement is the suggestion that its mechanism of action is like that of triiodothyronine.

Hsieh and Chiu (1959) observed that sodium salicylate administered intravenously to rats markedly increased oxygen consumption. The action prevailed in curarized animals. They suggest the possible stimulation of the hypothalamus, with the concomitant release of epinephrine, or a direct stimulating action by salicylate on tissue metabolism.

**Absorption, fate, and excretion of the salicylates.** Sodium salicylate is readily absorbed from the gastrointestinal tract. In many persons sodium salicylate is irritating to the gastric mucosa. Its irritant action is reduced by the simultaneous administration of equal quantities of sodium bicarbonate. Salicylates can also be absorbed from the skin when applied in the form of ointments. Methyl salicylate or oil of wintergreen is absorbed through the intact skin quite readily when it is applied with inunction in arthralgias (Brown and Scott, 1934).

After absorption, salicylic acid is carried to most of the tissues and organs of the body. Arthralgic joints do not show higher concentrations of the drug than other portions of the body. There appears to be no selective distribution of the drug either in rheumatic fever patients or in others using the drug for joint affections. Sodium salicylate or aspirin has been shown to be bound to plasma proteins in the blood. Batterman *et al.* (1962) demonstrated that in normal subjects salicylate is bound predominantly to albumin. In persons with abnormal electrophoretic patterns the binding of salicylate shifts from albumin to prealbumin fractions.

The main avenue of excretion for the salicylates is the kidney. Approximately 80 per cent of the drug is excreted in the urine. Alpen *et al.* (1951) studied the metabolic rate of salicylic acid in human subjects, using ($C^{14}$ carboxyl) salicylic acid. They found from 10 to 85 per cent of the salicylic acid excreted in the urine to be free salicylic acid. From 0 to 50 per cent of the salicylic acid excreted was eliminated as salicyluric acid. One per cent or less was excreted as gentisic acid and from 15 to 40 per cent as glucuronic conjugates. It was excreted also in sweat.

The excretion of salicylic acid begins within a half hour after its administration. The entire quantity of the drug (1 dose of 1 to 2 gm.) is excreted within 24 hours. Macpherson *et al.* (1955) observed that the rapidity of free salicylate excretion by the kidney is a function of the pH of the urine. The systemic acid-base balance is not the determining factor in salicylate excretion. The ratio of ionized to unionized salicylate increases with an increase in urinary pH, and greater quantities of salicylate are more rapidly excreted if the urine is rendered alkaline. They suggest that free salicylate is excreted by the process of tubular diffusion of unionized salicylate molecules rather than the more common method of glomerular filtration and tubular reabsorption.

Approximately 20 per cent of the ingested salicylic acid is oxidized in the tissues. In patients with rheumatic fever the percentage of the drug metabolized increases to a limited extent. A portion of the oxidized salicylic acid appears in the urine as *gentisic acid* (Lutwak-Mann, 1943). Gentisic acid is 2,5-dihydroxybenzoic acid. Meyer and Ragan (1949) observed that gentisic acid produced an effect similar to the salicylates when administered in rheumatic fever. They used a dosage of 10 gm. a day.

In massive doses it has been demonstrated in dogs (Barbour and Aydelotte, 1933) that salicylates are capable of exerting a nephrotoxic action. In man, proteinuria is occasionally seen with full therapeutic doses of salicylates in rheumatic fever.

**The untoward effects of the salicylates.** A comparatively large number of people show drug allergy to the salicylates. In some individuals skin rash is produced. Erythema, desquamation of the epidermis, and acne may occur. In others there is severe gastrointestinal distress with gastrointestinal bleeding. Other individuals experience tinnitus aurium and blurred vision of a transient character after the drug. In more susceptible persons a 300-mg. aspirin tablet may precipitate a violent respiratory reaction similar to an acute asthmatic attack. There is congestion of the nasal membranes. Frequently, edema of the eyelids, pharynx, and lips accompany the respiratory disturbance precipitated by the drug. The wise physician will avoid the use of salicylates in those individuals whose experience has taught them that they are idiosyncratic to salicylates.

Hemorrhagic tendencies sometimes follow the prolonged use of salicylates. It has been shown that this is due partially to hypoprothrombinemia produced by the drug. The diminished prothrombin of the blood produces a prolonged bleeding period. This along with peripheral vasodilatation is responsible for the salicylate hemorrhagic diathesis. To avoid this effect on the prothrombin level of the blood, menadione is recommended to be given with the prolonged administration of salicylates. This effect of 1 gm. of salicylate is counteracted by 1 mg. of menadione, page 698.

**Salicylate poisoning.** The appearance of "candy aspirin" for children has increased the number of intoxications from aspirin among children. Convincing data are available from the Chicago Poisoning Control Center. Of the first 500 cases reported to the center, 84 were attributed to aspirin and 73 of these 84 poisonings resulted from the ingestion of "candy" or "baby aspirin." This finding should enjoin the physician to warn against allowing these candy-like pellets of aspirin to be available in quantity to children. The problem of aspirin intoxication in children is of such urgency and so widespread that especially devised containers have been provided for "baby aspirin" with a rotating device which allows only the expulsion of one tablet at a time and requires a special adjustment of plastic wheels to eject additional tablets.

Oliver and Dyer (1960) conducted a control study on children who had ingested large doses of aspirin. They compared the effectiveness of early treatment with intravenous fluid and with fluid containing sodium bicarbonate. The clinical manifestations of salicylism subsided more rapidly in the patients receiving bicarbonate. A slight alkalosis resulted from the treatment but no untoward symptoms occurred. They recommended sodium bicarbonate administration early in the treatment of young children with salicylism.

In the treatment of salicylate intoxication there appear to be 3 principal foci of attack. The first is to combat the respiratory alkalosis, the second is to restore to normalcy the metabolic acidosis, and the third is to ameliorate the hypoprothrombinemia. To treat the respiratory alkalosis sodium is provided by the intravenous administration of isotonic sodium chloride solution. The infusion provides water and electrolyte so that renal compensation can ensue, and salt retention can be avoided. Calcium gluconate or brief inhalation of $CO_2$-$O_2$ mixtures is used to combat tetanic seizures if these are present.

The metabolic acidosis, if present as determined by the $CO_2$ content and pH of the blood, may be controlled with the intravenous administration of bicarbonate or lactate solutions. Small quantities of either of these solutions are administered with frequent checks on the $CO_2$ content and pH of the blood. Excessive amounts may precipitate respiratory alkalosis if salicylate blood levels are still high enough for continuing hyperpnea.

The hypoprothrombinemia is treated by the administration of adequate doses of vitamin K.

Most observers are of the opinion that opiates and barbiturates are contraindicated during the acute phase of salicylate intoxication. High blood levels of salicylates synergize the action of these sedatives, and coma may be induced.

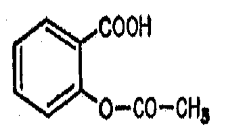
Aspirin intoxication usually results from the ingestion of coated tablets. Therefore, there is generally a time lag before absorption, which presents the opportunity of removal of a portion of the dose by gastric lavage or induced emesis. Inducing emesis immediately after contact with the patient will rid the gastrointestinal tract of a considerable proportion of the drug. Finger stimulated emesis or 15 ml. of syrup of ipecac is recommended. Mustard and salt water are less dependable, and copper sulfate, tartar emetic, and apomorphine are not without hazard when administered.

Furthermore, it has been pointed out by Done (1959) that salicylate plasma levels and clinical signs of intoxication do not always parallel each other. Cases are recorded with levels of 60 mg. per cent with no objective signs of intoxication, whereas others showed severe intoxication with levels as low as 22 mg. per cent. If clinical improvement is not achieved by treatment of the respiratory alkalosis and the metabolic acidosis, consideration should be given to hemodialysis or exchange transfusion. Sterne (1959) successfully used exchange transfusion in a 6-week old infant poisoned with aspirin. By means of 2 exchange transfusions, the plasma salicylate level was reduced from 35 mg. per cent to 23 mg. per cent, and the dyspnea and signs of intoxication were ameliorated.

**The therapeutic uses of the salicylates.** The general therapeutic uses of the salicylates have been already indicated. They are used to relieve integumental pain, headache, and to reduce fever. This action will be discussed further under the therapeutic use of aspirin. One of the main uses of the salicylates is in the treatment of rheumatic fever. This is discussed on page 840.

### ACETYLSALICYLIC ACID, U.S.P. (ASPIRIN)

Aspirin was synthesized in 1853 by von Gerhardt. Its introduction into medicine occurred in 1899. An employee of the Bayer Company in Elberfeld by the name of Felix Hoffman knew about the ester that was synthesized in the Bayer Laboratories. His father suffered with rheumatoid arthritis and did not tolerate well sodium salicylate. Hoffman tried aspirin on his father with success. This prompted the medical trial of aspirin by Dreser (1899) and by Wohlgemut in the same year. During the 20th century the popularity of aspirin has constantly increased. The structure of aspirin is shown in the accompanying formula.



Acetylsalicylic Acid, U.S.P. (aspirin)

Aspirin is a white powder, requiring about 300 parts of water for solution. In moist air it gradually decomposes into salicylic and acetic acids. It then acquires an acetous odor.

**The pharmacologic response to aspirin.** Aspirin is absorbed from the gastrointestinal tract. The acid of the stomach causes a partial hydrolysis of the ester. The ester circulates in the blood, and further hydrolysis occurs in that fluid. The action and use of aspirin are similar to those of sodium salicylate. The drug is believed to be more useful in the relief of headache than sodium salicylate.

Sodium salicylate appears to be more irritating to the gastrointestinal tract than aspirin. However, in some hypersensitive individuals aspirin produces gastrointestinal distress. When administered after meals, or when the agent is buffered, the incidence of this effect is materially reduced.

When 0.33 to 2 gm. of aspirin are ingested, the excretion occurs over 15 to 30 hours. Lester *et al.* (1946) showed that after taking 0.6 gm. of aspirin the maximal concentration was 4 mg. per cent in the blood. These workers showed that aspirin was rapidly hydrolyzed in the plasma. From 1 to 2 hours after administration 25 per cent still remained acetylated. Analgesia seems to be associated with the presence of the acetylated molecule in the blood. Plasma protein binds salicylate more readily than it binds the acetylated molecule. To establish adequate blood levels of aspirin for the relief of headache, neuralgia and myalgia, 0.6 gm. (2 tablets) seems to be the optimal dose for most individuals. One tablet is usually inadequate and 3 tablets appear to be unnecessary in most cases. The dose usually needs to be repeated every 2 to 3 hours. Batterman (1958) concluded from his studies that aspirin and buffered aspirin are absorbed at the same rate. Truitt and Morgan (1960) produced convincing evidence to show that (1) aspirin is partially absorbed from the stomach and (2) that the ingestion of two 5-grain aspirin tablets produced a peak plasma salicylate level of 2 mg. per cent in 30 minutes (average 30 subjects) and the ingestion of 2 Bufferin tablets yielded a peak level of 4 mg. per cent in the same time period. Their controls were adequate, and their data were subjected to a thorough statistical analysis.

Weikel (1958) studied the plasma levels of 3 analgesics in 6 subjects after the ingestion of 1 gm.; the drugs were aspirin, salicylamide, and N-acetyl-*p*-aminophenol. Aspirin yielded the highest peak level of 7 mg. per cent in 3 hours and was maintained for the longest period. Of interest is the fact that in 30 minutes the level of salicylate after aspirin was 2.1 mg. per cent which datum is in close agreement with the figure of Truitt and Morgan, namely, 2 mg. per cent after 0.6 gm. of aspirin in 30 minutes.

Felix Hoffmann
1868–1946

*A chemist with the Bayer Laboratories who first used aspirin on his father in the treatment of rheumatoid arthritis in 1899.*

Paul *et al.* (1950) studied the effect of various buffer systems on the rapidity of absorption of aspirin from the gastrointestinal tract. Their buffer system was composed of a mixture of magnesium carbonate and aluminum dihydroxyaminoacetate (*Bufferin*). The mixture of buffers when administered simultaneously with aspirin reduced the gastrointestinal distress in man. Gastric damage in rats with pyloric ligation (Shay rats) was also diminished. The rate of absorption of the salicylate from the gastrointestinal tract was increased 2-fold by the buffer mixture. Paul's studies provide experimental evidence of the use for aspirin and buffer mixtures in cases of gastrointestinal irritation. In addition, the onset of analgesia with aspirin may be hastened by this technic. Paul's observations were substantiated by Tebrock (1951 *et seq.*) among industrial workers. In over 1000 observations about 7 per cent of the subjects experienced gastrointestinal symptoms with aspirin, and approximately 2 per cent were so affected by buffered aspirin. The advantage of Bufferin in prolonged salicylate therapy in the treatment of arthritis was shown by Fremont-Smith (1955).

**Untoward effects of aspirin.** Aspirin is perhaps the most harmless analgesic available. The widespread use of the drug is some indication of its efficacy in headache and muscular pain. Besides, there are comparatively few cases of aspirin toxicity. This is all the more striking when one considers the immense daily tonnage consumption of aspirin by the American public. As a first approximation, the American public consumes 37 tons of aspirin daily.

One of the most frequently encountered untoward effects of aspirin is gastric irritation. This is often seen in patients with a history of gastrointestinal disease. The medical literature in the last half decade contains many reports of gastric irritation and hemorrhage from the ingestion of aspirin. Alvarez and Summerskill (1958) carried out a controlled study showing a definite relationship between salicylate consumption and massive gastrointestinal hemorrhage from peptic ulcer. Salicylates were incriminated in 40 per cent of 103 consecutive cases admitted to the hospital with hematemesis and/or melena associated with peptic ulcer. Summerskill and Alvarez (1958) encountered two cases of severe iron-deficiency anemia resulting from gastrointestinal hemorrhage due to habitual, heavy consumption of salicylates. Schneider (1957) carried out a double-blind study using aspirin, Bufferin, and a placebo in 19 subjects. In 6 of 10 subjects receiving 0.6 gm. aspirin, gross blood was noted in the gastric juice after ingestion of the drug. There was no change in gastric acidity. There was no bleeding in this group upon placebo medication. Bufferin caused a slight but significant rise in gastric acidity as compared to the placebo; but there was no bleeding in this group. It is clear that aspirin, especially when used repetitiously, should be given with caution to patients with established upper gastrointestinal disease. Furthermore, evidence seems convincing that the mucosal irritant action of the drug is mitigated by the simultaneous use of buffering agents.

Further studies involving 1,629 adult males confirmed the foregoing observations; 29.2 per cent revealed that they had experienced gastrointestinal distress after aspirin or aspirin mixtures (APC). When analyzing the data from 236 of the persons who experienced reactions from either product it was found that 33 per cent encountered reactions with APC, 18.3 per cent with aspirin, and 3.9 per cent with Bufferin.

There are numerous cases of aspirin allergy as it was stated under sodium salicylate. Dysart (1933) reported a case of death from a 5-grain aspirin tablet in a person who was allergic to salicylates. Death ensued in 5 minutes, a result of laryngeal edema. Cases of aspirin allergy are sufficiently common and serious to warrant the physician's attention.

Krasnoff and Bernstein (1947) reported the death of a 53 year old man following the repeated use of aspirin in the treatment of severe occipital headache. Upon autopsy the liver revealed hydropic and fatty degeneration with incipient necrosis. The kidneys showed renal congestion, glomerular and tubular degeneration. There were also lesions in the brain. Death followed within 3 hours after the ingestion of twenty 0.3-gm. aspirin tablets. There appears to have been cumulative damage done by the aspirin although symptoms did not manifest themselves until shortly before the fatal dose.

The treatment of salicylate poisoning is discussed on page 455.

### The therapeutic uses of aspirin.

1. The principal therapeutic use of aspirin is in the *relief of pain.* It is valuable in headache, neuralgia, and arthralgic pain. Its action is prompt and lasts for 2 to 3 hours after 0.6 gm. of the drug.
2. Like sodium salicylate, aspirin is used in rheumatic fever, p. 840. The use of aspirin in rheumatic fever and in rheumatoid arthritis has not waned despite the discovery of ACTH and the corticosteroids. The English "Empire Rheumatism Council Research Subcommittee" reported that in a 6-year study of cortisone acetate and aspirin, cortisone offered no advantage over aspirin. Although the immediate results with cortisone and ACTH are often dramatic, the long term effect of aspirin is equally efficacious and fraught with far less complications. Ansell *et al.* (1956) confirmed these findings in juvenile rheumatoid arthritis. Smith (1957) stated: "Medicine and the world at large are fortunate to have found a drug of these properties that are neither dangerous in moderate, but effective quantities, nor habit forming, as are narcotics."

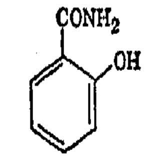
3. Aspirin is extensively employed in grippal conditions. Here there is no evidence to show that it aborts, lessens the course, or modifies the pattern of the affection. Its value is limited to the relief of pain and the reduction of fever, thus making the patient more comfortable. Paul (1959) holds the view that aspirin evokes a degree of mild sedation in many individuals which may be advantageous in some cases of insomnia.

### OTHER SALICYLIC ACID COMPOUNDS

*Oil of wintergreen is methyl salicylate.* It is used in liniments to apply to the skin. The use of the drug locally is accompanied by a strong psychogenic factor; however, upon inunction salicylate is absorbed through the skin.

*Phenyl salicylate* or *salol* was used formerly as an intestinal antiseptic. Its use is now outmoded.

**Salicylamide, N.F.** Salicylamide is the amide of salicylic acid as shown in the following formula:



Salicylamide, N.F.

Salicylamide occurs as a white powder which is quite insoluble in water but soluble in alcohol.

Salicylamide elicits the same character of analgesic and antipyretic response as does aspirin. Its potency appears to be of the same order of magnitude as that of aspirin or perhaps slightly less. It has been employed with impunity in patients who are sensitive to aspirin. The dosage is the same as that of aspirin.

Salicylamide is rapidly absorbed from the gastrointestinal tract; it is widely distributed through the tissues and is excreted by the kidneys for the most part unmodified or conjugated with glucuronic acid. Weikel (1958) gave salicylamide in 1-gm. doses to 5 subjects. Salicylamide reached a serum-level peak of 1.9 mg. per cent in one hour. Of special interest was the fact that no free salicylamide was present in the serum, all of the compound circulating in the blood was conjugated. Foye *et al.* (1959) investigated the urinary products of excretion in stone-forming patients who received 2 to 3.6 gm. of salicylamide. Approximately 46 per cent of the compound was excreted as the glucuronide and 31 per cent as the sulfate. Free salicylamide was excreted in 50 per cent and salicyluric acid in 40 per cent of the cases in undetermined quantities. In general, the salicylamide glucuronide excreted was the ether, but when the excretion of glucuronide was high, some ester was excreted also.

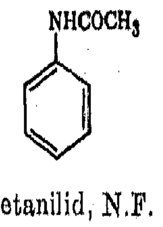
Vignec and Gasparik (1958) conducted a comparative study on the effectiveness of salicylamide and aspirin as antipyretics in infants. Each agent was found to be equally effective.

Salicylamide exhibits some central depressant action (Hart, 1947). Berger (1954) found that mixtures of salicylamide and acetophenetidin, which in themselves did not produce hypnosis in mice, when combined and injected elicited marked hypnotic activity. White *et al.* (1956) confirmed this finding and found that this hypnotic action of combined analgesics prevailed with salicylamide and acetanilid and also N-acetyl-*p*-aminophenol. When the salicylamide and N-acetyl-*p*-aminophenol were administered to patients in large doses using the "double blind" method, evidence of sedation was observed. This feature of the action of salicylamide does not obtain with aspirin.

A double blind study conducted by Boyd *et al.* (1957) on the hypnotic value of a mixture of 250 mg. of salicylamide and 100 mg. of acetophenetidin showed the combination to be effective in about 75 per cent of 157 hospitalized patients. One to 4 tablets of the foregoing mixture were used in place of the generally employed hypnotics, *e.g.*, chloral hydrate, paraldehyde and barbiturates. No significant side effects were noted. It does appear that this drug combination has merit, eliciting a mild hypnotic action, with concomitant analgesia and accompanied by a low habituation risk.

### ACETANILID, N.F.

Acetanilid is one of the oldest (1886) of the antipyretics and analgesics employed in medicine. Its structure is shown in the accompanying formula



Acetanilid, N.F.

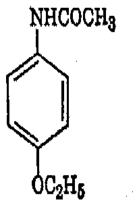
Acetanilid occurs as white, shiny crystals or as a white, crystalline powder. One part of acetanilid dissolves in 190 parts of water.

**Pharmacologic action of acetanilid.** Although acetanilid was used first as an antipyretic, its use today is confined largely to its analgesic action. The mechanism of action of the compound in relieving pain follows the general pattern of the analgesics of this series, *i.e., it raises the threshold to pain stimuli relayed from the thalamus to the cortex.*

The analgesic action of acetanilid appears to be greater than that of aspirin. In each case the analgesia varies with the dosage within the limits of therapeutic use. Thus, in mild headache or muscular pain 0.2 gm. of acetanilid is approximately as potent as 0.3 gm. of aspirin. Owing to the fact that acetanilid upon repeated doses produces methemoglobin formation, its use has been practically abandoned. For a detailed description of the drug see the 5th edition, page 708.

### ACETOPHENETIDIN, U.S.P. (PHENACETIN)

Acetophenetidin was introduced into medicine in 1887, and for many years it remained one of the most generally used nonaddictive analgesics. However, recent observations indicate that acetophenetidin upon repeated administration may be nephrotoxic and in certain sensitive individuals evoke hemolysis. Recently, its widespread use has diminished. It is para-ethoxyacetanilid as shown in the accompanying formula.



Acetophenetidin, U.S.P.

Acetophenitidin occurs as white, glistening crystals or as a white, crystalline powder. It is odorless and stable in air. One gram of acetophenetidin dissolves in about 1300 ml. of water.

**Pharmacologic action of acetophenetidin.** Like acetanilid, acetophenetidin is an antipyretic and analgesic. The presence of the ethoxy group in the molecule diminishes the toxicity of the compound especially with respect to the effect on hemoglobin. The analgesic and antipyretic actions of acetophenetidin are comparable to those of acetanilid.

As an analgesic, acetophenetidin appears to be about as active as aspirin. Its dose is the same as aspirin as a mild analgesic, namely, 0.3 gm. Acetophenetidin through the years has been proved effective in the relief of headaches and generalized pains in muscles and joints. It is most frequently used in conjunction with aspirin and caffeine.

Brodie and Axelrod (1949) elucidated the metabolism of acetophenetidin. The first step in its degradation is de-ethylation with the formation of N-acetyl-*p*-aminophenol. This latter compound is excreted in a conjugated form. Only a small portion is deacetylated to form *p*-phenetidin. Paraphenetidin was shown to be the precursor of the substance which oxidizes hemoglobin to methemoglobin. These investigators found that the analgesic and antipyretic actions of acetophenetidin are elicited mainly by N-acetyl-*p*-aminophenol. This substance was found to produce analgesia. The highest blood levels of acetophenetidin occur about 2 hours after ingestion, little remains in the body after 5 hours. The metabolite of acetophenetidin, N-acetyl-*p*-aminophenol, when administered is absorbed more rapidly, and after 30 minutes brain and plasma concentration are approximately the same. This suggests the rapid passage of this metabolite into the central nervous system after oral ingestion. N-acetyl-*p*-aminophenol is used as an analgesic and antipyretic similar to acetophenetidin. It is a white crystalline powder which is soluble 1 in 73 in water. From the foregoing discussion it is clear that the advantage offered by N-acetyl-*p*-aminophenol is a more rapidly acquired peak plasma level after ingestion. The dosage range is usually 300 to 600 mg. There are many proprietary forms of this compound available in which the drug is mixed with caffeine, aspirin, and salicylamide in various proportions.

As previously indicated recent observations regarding the chronic toxicity evoked by acetophenetidin have caused its use as an analgesic to wane. Evidence indicates that daily doses of 1 gm. or more taken over a period of several months have occasionally produced methemoglobinemia, sulfhemoglobinemia and hemolytic anemia. In addition, the repetitious use of the drug is believed to evoke severe renal injury, *i.e.,* chronic interstitial nephritis with papillary necrosis. The latter toxicity develops insidiously and may be fatal (Moolten and Smith, 1960). MacGibbon *et al.* (1960) suggest that red blood cells with adsorbed acetophenetidin may act as antigens, producing autoantibodies, leading to acute hemolytic anemia and acute renal failure.

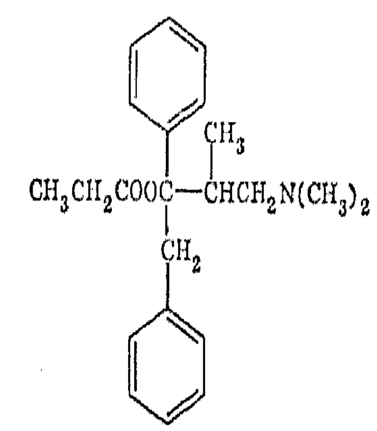
In light of these observations, some of the proprietary analgesics containing acetophenetidin have been modified by removing the acetophenetidin and replacing it with an equal quantity of aspirin. It would therefore be prudent if acetophenetidin is prescribed, and there appears to be no crucial demand for its use, that its dose be limited and the duration of treatment be short.

**Headache remedies.** For many years acetophenetidin took the place of acetanilid in most of the well-known and popularly advertised headache powders. In view of recent observations regarding its toxicity, acetophenetidin has now been replaced by aspirin in many headache remedies. In other proprietary forms acetophenetidin is mixed with aspirin and caffeine. This is the popular APC mixture. There is no convincing evidence to indicate that the mixture of the 2 analgesics is more effective than an adequate dose of aspirin. Nevertheless, there are many people who ingest the combination APC who feel that it is superior to aspirin (Cass and Frederik 1962). Caffeine has been used for years in headache powders. It is not an analgesic. It has not been shown to potentiate the analgesia produced by aspirin and similar drugs. Its value, if any, in these headache powders is possibly due to slight cerebral stimulation. This appears to be a definitive factor in suppressing the awareness of pain.

### NEWER NONADDICTIVE ANALGESICS

There have been relatively few additions to the effective nonaddictive analgesics. Advances in this field of therapy have lagged behind the rapid advances achieved in other areas. Within the last half decade 2 interesting additions have been added to the armamentarium as nonnarcotic analgesics; they are Darvon (dextro propoxyphene hydrochloride) and ethoheptazine citrate. The latter compound has not appeared to be competitive as an analgesic, and its use has diminished. For a description of the drug see the 5th edition; page 712.

**Dextro Propoxyphene Hydrochloride (Darvon).** Darvon was synthesized by Pohland and Sullivan in 1953. Its structure is shown in the formula.



Dextro Propoxyphene Hydrochloride
Darvon

(*α-d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butyl propionate hydrochloride)

There are 4 stereoisomers, of these Darvon alone evokes analgesic activity. Levo propoxyphene (Novrad) is not an analgesic but elicits an antitussive action. Darvon is a white crystalline powder which is readily soluble in water.

**Pharmacologic response to Darvon.** The principal pharmacologic response elicited by Darvon is that of analgesia. Analgesia in animals is perceptible upon the oral administration of the drug at a level of 2.5 mg./kg.; the $LD_{50}$ is 185 mg./kg. indicating a wide margin of safety. Long term feeding experiments revealed no damage to the viscera of animals or alterations to the elements of blood. Respiratory depression is produced with intravenous infusions in dogs at 25 per cent of the lethal dose. Alterations in the circulatory system occurred in these experiments only sequentially to the approaching terminal respiratory arrest. Subsequent trials in man have confirmed the comparative innocuous nature of Darvon.

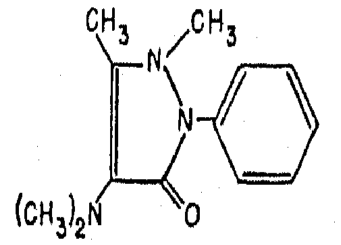
The mechanism of action of its analgesic effect has not been delineated. Because the drug elicits no addictive hazard and does not modify mental alacrity, the principal site of its response is likely subcortical. Because its principal field of value in man is in mild to moderately severe pain (myalgias, neuralgias, arthralgias etc.) and not in deep seated visceral pain, it is suggestive of a lateral spinothalamic pathway blocking action similar to that of the other nonaddictive analgesics.

**Clinical studies with Darvon.** Numerous clinical studies with Darvon have testified to its efficacy as an analgesic. The degree of the analgesia produced by Darvon appears to be about equal to that evoked by codeine. Gruber (1957) studied Darvon in 101 hospitalized patients with pain from chronic diseases. His data were gleaned from 1515 daily reports. He concluded that Darvon gave rise to an analgesic action tantamount to that of codeine phosphate when each drug was given in 65 mg. doses. There were fewer side effects with Darvon and tolerance was not acquired. Of special mention is the fact that Darvon, unlike codeine, is not constipating. The duration of analgesia with each drug was found to be approximately 6 hours. There appear to be no specific contraindications to the use of Darvon.

This comparatively new drug has already had wide acceptance by the medical profession. Its adult dose is 32 to 65 mg. every 4 hours. It is also available mixed with other analgesics, such as aspirin, acetophenetidin, and caffeine for other areas of therapy such as grippal conditions and arthritis. The success of Darvon as a new type of chemical structure for a non-narcotic analgesic should serve as a definitive impetus for further investigations into this fertile field.

### AMINOPYRINE

Aminopyrine was introduced under the trade name of *Pyramidon*. It was prepared as a derivative of the first synthetic antipyretic *Antipyrine*. So superior to antipyrine is its derivative aminopyrine that the latter drug has almost completely replaced the former. Antipyrine evokes a local anodyne action and is a constituent of several preparations used as collyria and for application to the external ear. The structure of aminopyrine is shown in the accompanying formula.



Aminopyrine
(4-dimethylamino-2,3-dimethyl-phenylpyrazolone)

Aminopyrine occurs as white, small crystals or as a white, crystalline powder. It is soluble in 18 parts of water.

**Pharmacologic action of aminopyrine.** Aminopyrine is the most powerful analgesic and antipyretic in this series of drugs. It is rapidly absorbed from the gastrointestinal tract and promptly evokes its pharmacologic response. The usual dose is 0.3 gm. Aminopyrine is effective, similar to salicylates, in the treatment of the acute phase of rheumatic fever. Balsam and Katz (1961) found aminopyrine effective in the treatment of diabetes insipidus. The drug appeared to evoke a water and salt retaining action that ameliorated the symptoms of the disease. They found it a useful adjunct to vasopressin therapy. It was estimated that 2 gm. of aminopyrine administered orally was as effective as 1 ml. of vasopressin given intramuscularly.

In man, aminopyrine is demethylated to form 4-aminoantipyrine. This metabolite is an analgesic. This substance is acetylated, forming an inert compound. A small fraction of aminopyrine is converted to 4-hydroxyantipyrine which is excreted in a conjugated form. The fate of approximately one-half of the ingested aminopyrine has not been determined (Brodie and Axelrod, 1950).

**Minor untoward actions of aminopyrine.** Aminopyrine has been known to produce gastrointestinal distress, skin rashes, and tremors.

**Aminopyrine and agranulocytosis.** Kracke (1931) and Madison and Squier (1933) made the observation that agranulocytosis was frequently associated with a history of antipyrine or aminopyrine medication. At that time there were no restrictions on the sale of aminopyrine, and it was present in many of the most effective headache remedies. This status of aminopyrine prevails in many European countries today where its use is similar to the use of aspirin in the United States.

Many drugs in use in the 1930s were suspected of causing agranulocytosis, but it appears that about 80 per cent of the clinical cases were associated with aminopyrine medication (Kracke, 1938).

The effect of aminopyrine in producing agranulocytosis is in the nature of a drug allergy. The effect may follow the administration of a single therapeutic dose of the drug. On the other hand, it may occur suddenly after a person has used the drug for long periods of time. In susceptible persons aminopyrine produces pathologic changes in the bone marrow.

Parker and Kracke (1936) found that quinone and hydroquinone were active in producing leukopenia in rabbits. They proposed that in idiosyncratic persons the aminopyrine may undergo oxidation, forming quinone. However, Kracke (1938) failed to produce leukopenia in rabbits, guinea pigs, rats, and dogs by the administration of aminopyrine orally or parenterally.

Davis and Frissell (1937) used aminopyrine on 32 rheumatic patients. They gave 2 gm. a day for 2 weeks to 3 months. They found no change in the leukocyte count.

Dameshek and Colmes (1936) concluded that the incidence of agranulocytosis in users of aminopyrine occurred once in 10,000 persons. The subcommittee on blood dyscrasias of the American Medical Association revealed 6 cases of blood dyscrasias owing to aminopyrine and 14 in which it may have been a contributing factor during the period 1956–1959. The same committee reported 45 cases in which the ingestion of acetophenetidin, aspirin, and caffeine (APC) was causally related to blood dyscrasias. The clinical impression of Madison and Squier (1934) that agranulocytosis is more frequently encountered when aminopyrine is administered with a barbiturate is a precautionary measure that should be heeded when aminopyrine is prescribed.

Agranulocytosis is heralded by a pharyngitis and mucous membrane changes similar to Vincent's angina. At the first sign of throat irritation or swelling when an individual is taking aminopyrine, the blood picture should be examined and the drug withdrawn. The ulcerative membranes of the throat associated with an extraordinarily low white cell count is diagnostic of the disease.

**Phenylbutazone (Butazolidin).** This compound is an aminopyrine derivative used principally in the treatment of arthritis. It is discussed on page 845.

**Neocinchophen, N.F.** This analgesic is discussed under the treatment of gout, page 826.

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# 30

# *Central Nervous System. Anti-Motion Sickness Drugs*

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**Nature of motion sickness.** The expression *motion sickness* to designate a syndrome of vertigo and nausea resulting from body motion was used first in 1881. Motion sickness is a specific disorder which is produced in animals and susceptible persons when they are subjected to movements which have certain characteristics. Prior to World War II factual information regarding motion sickness was meagre. It was agreed that the vestibular apparatus was involved in the syndrome, and further, that in ships, linear rather than angular accelerations were the more effective incriminating stimuli. It became imperative during the war to investigate the problem as large forces of men had to be transported by land, sea, and air under all types of circumstances. New information has been acquired and certain drugs have been developed to combat the syndrome with reasonable success (Tyler and Bard, 1949).

The symptoms of motion sickness vary in different individuals; however, the following symptoms are usually encountered: *drowsiness; pallor; cold sweating; salivation; nausea; epigastric awareness;* and *vomiting. Headache* and *vertigo* are also often present.

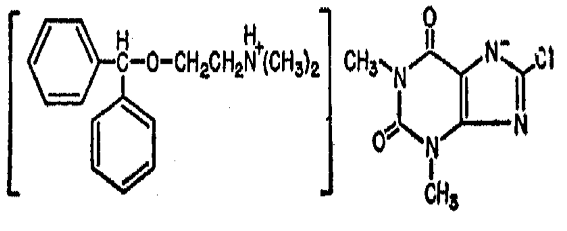
The symptoms likely result from the sense organs of the labyrinth, the semicircular canals or utricle that are stimulated by motion, generally linear acceleration or deceleration. Reflexes are set up through the vomiting center, and the autonomic centers are responsible for the symptoms. Unless vomiting prevails for a considerable period of time, no special changes in blood chemistry occur.

**Earlier drugs used in motion sickness.** The belladonna alkaloids have been found quite effective in relieving motion sickness. During World War II, atropine, hyoscyamine, and hyoscine were studied extensively. Of the 3 alkaloids, it appeared that hyoscine was the most effective, and this may be associated with its depressant effect upon the higher cerebral centers.

**The discovery of dimenhydrinate in the treatment of motion sickness.** Gay and Carliner (1949) wrote with regard to the discovery of dimenhydrinate. "Among other patients, the drug was administered to a pregnant woman with urticaria, who incidentally had suffered all her life from car sickness. It was possible to control the car sickness of this patient at will. A placebo failed repeatedly, but dimenhydrinate gave complete relief if she took 50 mg. a few minutes before she boarded the street car." Dimenhydrinate had been prepared for these investigators as a type of antihistaminic drug combining diphenhydramine and theophylline. It was through their keen clinical insight and vigil that they observed its possible usefulness in the treatment of motion sickness.

After some preliminary trials on susceptible individuals, an extensive study was instituted on troops by the Army Transport Service. The observations of Gay and Carliner were confirmed in the main and the drug has been shown to be both prophylactic and curative.

**The nature of Dimenhydrinate, U.S.P. (Dramamine).** Dimenhydrinate is β-dimethylaminoethyl benzhydryl ether 8-chlorotheophyllinate. The chlorination of theophylline in position "8" increases its acidic dissociation. This achieves the combining of it chemically with the amine β-dimethylaminoethyl benzohydryl ether (diphenhydramine). The structure of the salt is shown in the accompanying formula. The substance occurs as a white powder relatively insoluble in water. The salt contains 54.3 per cent of diphenhydramine.



Dimenhydrinate, U.S.P.
Dramamine

**Dimenhydrinate and diphenhydramine.** The effectiveness of dimenhydrinate in motion sickness posed the obvious question as to which part of the molecule was responsible for the protective action, namely, diphenhydramine or 8-chlorotheophylline. Chinn and Oberst (1950) studied the effect of diphenhydramine and 8-chlorotheophylline on subjects in preventing air sickness. Doses of 50 mg. were given before take-off. No significant difference in protection was observed between 50 mg. of diphenhydramine and 100 mg. of dimenhydrinate. 8-Chlorotheophylline in 50-mg. doses afforded only slight protection as compared with a placebo. These investigators used a combination of 50 mg. of diphenhydramine and 0.65 mg. of hyoscine hydrobromide for protection and found the mixture to be more effective than either drug alone.

**Dimenhydrinate in motion sickness.** It is apparent that the active constituent of the dimenhydrinate molecule is the diphenhydramine portion. Diphenhydramine exhibits a definite anticholinergic action similar to atropine. Its spasmolytic action antagonizes the gastric hypermotility and gastric hypersecretion of motion sickness. Its action opposes bronchial constriction and like atropine, produces a greater tidal volume. Diphenhydrinate also elicits a definite although transient stimulation of respiration.

Hyoscine appears to be the most effective anti-motion sickness drug of the belladonna series. It definitely produces cerebral depression. Diphenhydrinate shares this action and in many individuals produces a drowsiness, desire for sleep, and actually serves as a soporific.

Wang and Chinn (1954) established that experimental motion sickness produced in dogs by prolonged swinging of the animals could be abolished in most cases if the *chemoreceptive emetic* trigger zone was previously ablated. This zone lies in the floor of the fourth ventricle at the level of the calamus scriptorius and has been identified as the lateral portion of the *area postrema*. When this area is destroyed dogs will not vomit when given apomorphine and in most cases are refractory to motion sickness.

In dogs which have been given a threshold dose of apomorphine to produce vomiting, emesis can be mitigated and even checked by diphenhydramine. Thus it appears that the trigger zone of the vomiting center is rendered less sensitive to stimuli by diphenhydramine.

It therefore becomes apparent that the use of diphenhydramine or dimenhydrinate in motion sickness offers little novel in therapy. The atropine-like action and sedative properties were used for years in the treatment of the syndrome and were elicited by hyoscine or hyoscine and a barbiturate. Diphenhydramine appears to combine these properties effectively. If 8-chlorotheophylline contributes to this effect it apparently has not yet been demonstrated.

**Clinical uses of dimenhydrinate.** Since the use of dimenhydrinate in motion sickness was first observed by Gay and Carliner, the drug has been used extensively for prophylaxis in sea sickness for sea voyages and fishing trips. It is used routinely now on airplanes and appears to be affording excellent prophylaxis against these forms of motion sickness. The only untoward effect reported by a considerable segment of those using the drug is drowsiness. The drowsiness is often described as a pleasurable drowsiness. In motion sickness the use of the drug appears to be well established as a prophylactic and curative agent. Its usual dose is 50 to 100 mg. in tablet form.

In the treatment of the nausea of pregnancy the use of dimenhydrinate has been found effective. Carliner *et al.* (1949) gave 100 mg. 3 times a day to 43 women whose pregnancy was accompanied by nausea and vomiting. Seventy-two per cent experienced complete relief of the symptoms upon the administration of dimenhydrinate. The experiment was well controlled. Some of the patients suffered from vague subjective muscle tremors with the therapy.

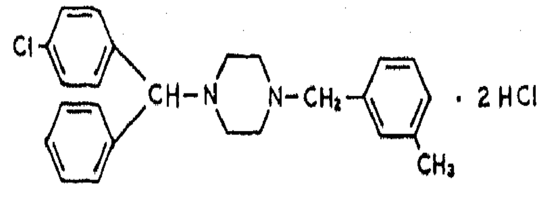
The successful prevention of nausea after electric shock therapy by the administration of 100 mg. of dimenhydrinate 1 hour prior to treatment has been reported.

Dimenhydrinate has been useful also in reducing the incidence of nausea following anesthesia. Moore *et al.* (1955) critically studied the use of dimenhydrinate postoperatively in more than 9000 cases. These involved many types of surgical procedures and most of the usual anesthetic agents. Dimenhydrinate was given intramuscularly 50 mg. upon call to surgery, 50 mg. after surgery, and 50 mg. every 4 hours for 4 additional doses. In a segment of the study the "double blind" procedure was used to rule out bias. They concluded from the results of this study that dimenhydrinate so administered reduced postoperative vomiting 50 per cent.

Campbell (1950) used dimenhydrinate in patients to relieve the vestibular reactions following the labyrinth fenestration operation. He observed a moderate degree of reduction of postoperative symptoms of vertigo, nausea, vomiting, and nystagmus.

Rotter *et al.* (1958) used dimenhydrinate intravenously to diminish the time of labor and to potentiate analgesia. The drug was given to the patients who presented a cervical dilation of about 2 cm. and intact membranes in whom the active contractions of the first stage of labor was established. The average length of labor of the dimenhydrinate-treated patients compared with a control series was decreased by 3.13 hours in the primiparas and 2.7 hours in the multiparas. The decrease in the period of labor was attributed to the relaxation elicited by dimenhydrinate. The dosage level of sedatives required was also decreased in the patients treated with dimenhydrinate.

**Meclizine Hydrochloride (Bonine, Postafene).** Bonine has been used most successfully in the prophylaxis and treatment of motion sickness. Its structure is shown in the following formula:



Bonine (Meclizine Hydrochloride)
(*p*-chlorbenzhydryl)-4(*m*-methylbenzyl)piperazine dihydrochloride)

Bonine occurs as a white crystalline powder which is insoluble in water but slightly soluble in acidulated hot water.

Bonine is a drug with especially long-acting anti-motion sickness properties. One dose per day is quite effective in seasickness, and a single dose given before sailing or 24 hours before flying is effective against motion sickness.

Handford *et al.* (1954) screened several anti-motion sickness drugs in a large-scale study among military personnel. They found Bonine and Dramamine effective and quite devoid of side effects. Bonine afforded longer periods of protection. An interesting observation in the study was that predisposition to motion sickness decreased with the increasing age of the subjects. The value of Bonine for prophylaxis against motion sickness has been confirmed by a joint committee of U. S. Army, Navy and Air Force (1956).

The dose of Bonine is 25 to 50 mg. daily for adults. Children require about ½ of the adult dose. Bonine, like other antihistaminic agents, may produce drowsiness, fatigue, blurred vision, and xerostomia in certain individuals. Therefore caution should be urged in the operation of motor vehicles after motion sickness prophylaxis with Bonine. It is our observation that Bonine is quite devoid of any side effects in most people who use it to avoid motion sickness.

Franks *et al.* (1962) compared the efficacy of meclizine (Bonine) with meprobamate in air sickness in over 400 airmen. Meprobamate was given at doses of 400 mg. and meclizine at 50 mg. 2 hours before flight. The test was adequately controlled by the administration of placebos. They found meprobamate as effective as meclizine and a combination of the 2 drugs more effective than either given alone.

Bonine is also useful in the treatment of nausea and vomiting of pregnancy. For this purpose it is usually given with pyridoxine hydrochloride 50 mg. The mixture is known as Bonadoxin.

**Bonadoxin** has been used successfully in the treatment of nausea following therapeutic irradiation. Relief has been experienced in about ¾ of the patients.

TABLE 30-1

*Drugs Effective in the Prophylaxis of Motion Sickness*

| Drug | Dose* |
|---|---|
| | *mg.* |
| Benztropine (Cogentin) methanesulfonate | 1.0 |
| N-Benzhydryl-N-*m*-methylbenzylpiperazine (UCB 158) | 50 |
| Buclizine (Vibazine) hydrochloride | 50 |
| Cyclizine (Marezine) hydrochloride | 50 |
| Dimenhydrinate (Dramamine) | 100 |
| Diphenhydramine (Benadryl) hydrochloride | 50 |
| Diphenhydramine (Benadryl) hydrochloride | 25 |
| *plus* Scopolamine hydrobromide | 0.35 |
| Ethopropazine (Parsidol) hydrochloride | 50 |
| Meclizine (Bonine) hydrochloride | 50 |
| 1-Methyl-4-amino-N′-phenyl-N′-(2′-thenyl)-piperidine tartrate (Sandostene) | 50 |
| Pheniramine (Trimeton) maleate | 25 |
| Promethazine (Phenergan) | 25 |
| Scopolamine hydrobromide | 0.75 |

* Dose given 3 times a day for seasickness prophylaxis except Bonine, which was effective when given once a day, and Phenergan, which was effective when given twice a day.

The extensive investigations of Tower (1956 *et seq.*) have demonstrated the importance of pyridoxine in neuronal metabolism. In its coenzyme form it is essential to the activity of a number of enzyme systems in the brain. A deficiency of pyridoxine disturbs the metabolism of neuronal lipids of myelin structures and has been shown to evoke convulsive seizures. It is likely that this important metabolic neuronal function of pyridoxine is a factor in providing relief from nausea and vomiting of pregnancy and therapeutic irradiation.

Almost all drugs used for the treatment of motion sickness produce drowsiness in a certain segment of the population. Chinn *et al.* (1953) showed that the addition of 5 mg. of dextroamphetamine as a prophylactic to a mixture of diphenhydramine and scopolamine does not diminish significantly the effect on airsickness. Depression, however, is diminished.

**Cyclizine Hydrochloride (Marezine).** Marezine is another one of the anti-motion sickness drugs which appears to be gaining favor. Chemically, Marezine is N-benzhydryl-N′-methylpiperazine hydrochloride. It occurs as a white crystalline powder which is soluble in water.

The action of Marezine is similar to that of dimenhydrinate and Bonine. It does not elicit drowsiness, xerostomia, or blurred vision as side effects. The dose as indicated in table 30-1 is 50 mg., 3 times a day to prevent motion sickness.

Marezine is also available in rectal suppositories containing 100 mg. of the drug. This affords an excellent method of administration for the reduction of postanesthetic nausea. For example, Bonica *et al.* (1958) used Marezine for this purpose in a series of 2827 patients. Of these patients, 22.3 per cent manifested symptoms of retching and/or vomiting and 5.4 per cent experienced nausea only. The over-all incidence of emetic symptoms was 27.7 per cent. In a controlled study, Marezine administered in suppository form afforded relief in 93 per cent of the patients compared with 60 per cent relief afforded by a placebo suppository. The relief was accomplished with a minimal incidence of side effects. This procedure is a comparatively simple and safe method of significantly reducing the gastrointestinal distress which often follows anesthesia.

Cramer and Dowd (1962) studied the effect of Marezine in decerebrate and decerebellate cats in single cells of the vestibular system. The drug was given by vein and the cells stimulated electrically through the window of the ear. There was no difference in cellular activity before and after Marezine. They concluded that since the drug exerts no effect upon the vestibular nerve or on the primary vestibular nuclei, its value in motion sickness stems from its action on other parts of the central nervous system.

**Other drugs in motion sickness.** Many other drugs have been tried recently in sea and air sickness. Some of these show excellent promise. A joint committee of the United States Army, Navy and Air Force, using a total of 16,920 soldiers and airmen crossing the North Atlantic aboard transport ships, found that 11 compounds gave significant protection. Of the effective agents, the use of 50 mg. meclizine, once or 3 times daily, 50 mg. of cyclizine, 3 times daily, and 25 mg. of promethazine, 3 times daily, was significantly more effective than use of other drug regimens.

Table 30-1 lists drugs that have been shown to be effective in preventing sea sickness. Most of these drugs have been shown to prevent air sickness when a single dose of the drug is given prior to flight. As stated previously there is evidence that Bonine, Marezine, and Phenergan are the most effective, at least for sea sickness.

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# 31

## *Central Nervous System Stimulants*

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Thus far we have considered the depressants of the central nervous system. These drugs are among the most important in the physician's armamentarium. Indeed, the pharmacologic efforts to produce sedation and unconsciousness, allay convulsions, and relieve pain have been strikingly successful. The same degree of success has not been achieved among the central nervous system stimulants. The drugs of this class, which are valuable as therapeutic agents, are few indeed when compared with the formidable list of depressants.

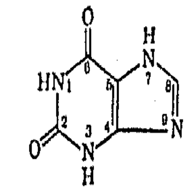
**Use of stimulants to the central nervous system.** The stimulants to the central nervous system that act upon the sensory areas in the brain are used to increase alertness, brighten the spirits, and combat mental fatigue. In this class are the therapeutic agents, caffeine and Dexedrine. Those agents which act directly or reflexly on the centers of respiration are used in threatened collapse of the respiratory mechanism. They are used in narcotic poisoning, near drowning, and threatened collapse under anesthesia. To this class of agents belong nalorphine, pentylenetetrazol, and nikethamide.

In the treatment of mental illness, characterized by depression, a new class of drugs has been developed called the *antidepressives*. These include the monoamine oxidase inhibitors and other drugs that do not combat depression through this mechanism (page 518).

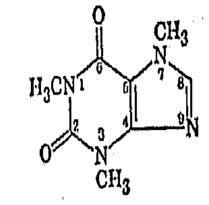
Another category of stimulants of the central nervous system is typified by the spinal stimulant strychnine. Although the drug has been used for years empirically in a variety of maladies, there seems to be no scientific basis for the use of this spinal stimulant in medicine.

### Caffeine, U.S.P.

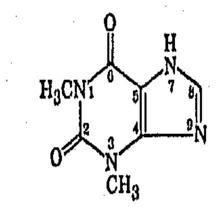
Caffeine is a xanthine derivative found in tea, coffee, and other plants. It is also made synthetically. There are 3 xanthine bases used medicinally: theophylline, theobromine, and caffeine. Their chemical constitutions are shown in the accompanying formulas.



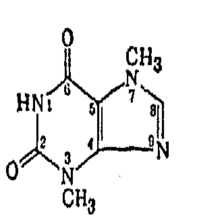
Xanthine



Caffeine
(1,3,7 trimethyl xanthine)



Theophylline
(1,3 dimethyl xanthine)



Theobromine
(3,7 dimethyl xanthine)

Caffeine is present in the seeds of *Coffea arabica* to the extent of about 1 per cent. The leaves of *Thea sinensis* contain theophylline and caffeine amounting to about 3 per cent. The seeds of *Theobroma cacao*, the chocolate plant, contain theobromine. The 3 methylated xanthines evoke similar pharmacologic responses. They differ, however, in the degree of their response on different tissues. In the main the compounds are:

1. Cerebral stimulants
2. Coronary and bronchiolar dilators
3. Diuretics

Other actions include cardiac stimulation and respiratory stimulation. Considering the 3 main actions of the methylated xanthines, caffeine is preferred for cerebral stimulation. Theophylline is the drug of choice for coronary and bronchiolar dilatation. Theophylline exceeds theobromine in its acute diuretic action, but the diuresis of theobromine is more prolonged, and therefore it is the diuretic which is generally preferred in the group.

Theophylline will be discussed under the pharmacology of the circulation, page 670, and theobromine will be considered in the section on water balance, page 811. Caffeine as a cerebral stimulant will be the subject of this section.

**Properties of caffeine.** Caffeine occurs as a white, glistening powder. It is odorless and elicits a bitter taste. One gram of caffeine dissolves in 50 ml. of water. The solution is neutral. When caffeine is mixed with an equal weight of citric acid, *citrated caffeine* is formed, which is soluble in 4 parts of water. Caffeine is soluble in sodium benzoate solution. *Caffeine and sodium benzoate* is official, containing 50 per cent of *anhydrous caffeine*. The combination is soluble in 1.2 parts of water. It is the parenteral preparation of choice of caffeine.

**The effect of caffeine on cerebral centers.** The principal site of the action of caffeine on the central nervous system is the *sensory cortex*. Larger doses affect the motor areas, and the action descends to the medulla oblongata and the spinal cord. Therapeutic oral doses of caffeine produce an increased degree of irritability of the sensory cortex. This results in:

1. Increased mental alacrity
2. Alertness and brighter spirits
3. More acute and discriminating sensations
4. Facilitation of association of ideas
5. Retardation of action due to more discriminating judgment

6. Occasional insomnia—sleep may be disturbed by dreams in the uninitiated individual.

The foregoing actions of caffeine on the cerebral cortex have been demonstrated in laboratory animals and in observations on people trained to perform tasks such as typing and target pricking.

Dogs to which caffeine is administered show an exaggerated response to a standard electrical stimulation to the motor cortex. In man there is little evidence of increased motor activity produced by caffeine.

The question of a subsequent depression of cerebral activity after the stimulation produced by caffeine has been the subject of a great deal of study. It cannot be doubted that excessive doses of caffeine produce an excitability of the sensory cortex, a restiveness, a feeling of mental anxiety, which when passed leave a sense of depression in their wake. However, the mild physiologic type of cerebral stimulation evoked by caffeine does not appear to be followed by depression (Cheney, 1935). Although Horst *et al.* (1934) are of the opinion that caffeine does leave a feeling of depression, the evidence seems to indicate that it is difficult to differentiate the mild depression from normal mental fatigue after cerebral activity, and the depression, if any, is inconsequential.

Caffeine has been used widely in the treatment of headache. It is a frequent constituent of the generally-used headache remedies. Moyer *et al.* (1952) placed its therapeutic use in hypertensive headaches on a sound basis. Caffeine was shown to decrease the arterial and post-arteriolar vascular distension of cerebral vessels, and through this mechanism relieve hypertensive headaches. A decrease in cerebral blood flow was demonstrated.

This was followed by a reduction in cerebrospinal fluid pressure. The fall in cerebrospinal fluid pressure is secondary to the decrease in cerebral blood flow. Aminophylline shares this action with caffeine. Moyer and his associates found aminophylline to be the more effective of the two drugs in the relief of hypertensive headache. Sudden withdrawal from the ingestion of caffeine may give rise to headache. Caffeine tends to constrict the cerebral vessels, and heavy coffee drinkers who abruptly stop its use may experience headache from a rebound dilatation of the cerebral vessels.

**The effect of caffeine on the medullary centers.** The oral therapeutic dose of caffeine of 0.2 to 0.3 gm. produces no detectable effect on the medullary centers. When the drug is given parenterally, stimulation of the medullary centers occurs. Respiration is stimulated by the direct action of caffeine. Especially is this noticeable if the respiration has been acutely depressed by some drug antagonist such as chloral hydrate or morphine. On the other hand, when caffeine and sodium benzoate is given as a respiratory stimulant to check the failure of a respiratory mechanism which has been chronically poisoned for long periods, as in uremia, the drug produces little benefit. When the patient is in a moribund state and peripheral circulation is poor, the absorption of the caffeine is doubtful. In such cases the slow intravenous injection is the most dependable method of administration.

Richmond (1949) studied the effect of caffeine and aminophylline upon respiration in man. A dose of 0.25 gm. of caffeine and sodium benzoate was administered subcutaneously. While the subjects were breathing air, caffeine produced only an insignificant increase of 2.8 per cent in the ventilation volume. When the subjects were breathing 3 and 5 per cent carbon dioxide-oxygen mixtures, caffeine produced an increase of 23 and 51.7 per cent ventilation, respectively. Richmond concludes that since carbon dioxide acts directly on the respiratory centers and caffeine enhances this action, caffeine must render these centers more sensitive to carbon dioxide. This action was not shared by aminophylline.

**The effect of caffeine on the circulation.** When caffeine stimulates the respiratory centers, it also stimulates the vagus center. The cardiac slowing which would be produced through vagal action is antagonized by the direct stimulation of the drug on the myocardium. The vasoconstrictor center is also stimulated, but simultaneously the peripheral vessels are dilated by the direct musculotropic action of caffeine. The overall effect is a slight transient fall in blood pressure. This is observed most strikingly when the drug is given rapidly by vein.

Starr *et al.* (1937) observed that caffeine evoked a slight increase in cardiac output. Schök (1950) administered caffeine in 50 and 100 mg. doses to hypertensive patients. He observed a fall in systolic and diastolic blood pressures. With normotensive persons the effect of caffeine on the blood pressure was variable.

**The effect of caffeine on skeletal muscle.** When caffeine solutions are applied to teased muscle, microscopically the contents of the fibers are seen to move, the cross striations disappear, and the longitudinal striae become more prominent. The sarcolemma becomes detached. Caffeine has been considered a muscular stimulant. At the lowest concentrations at which the drug is effective, it is said to increase the amount of work that a muscle can do. Higher concentrations reduce the work. Indeed experiments on isolated frog's gastrocnemius muscle show that caffeine in optimal concentrations increases the tension output (Saslow and Webster, 1935). At an enzyme level caffeine was found to be ineffective on muscle catalase. Caffeine exhibited a definite inhibitory effect on muscle adenosine triphosphatase and nerve cholinesterase. Bianchi (1962) using radiocaffeine showed that when the alkaloid enters the sartorius muscle of the frog it occupies the space approximately equal to or greater than the water space. Caffeine is not bound by the tissue and is readily removed by washing.

The increased activity of skeletal muscle after caffeine appears to be central in origin and possesses a strong psychogenic component. Theobromine has the most striking effect on isolated skeletal muscle of the 3 methylated xanthines. Yet, because of its comparatively weak cerebral effect, its action on muscle activity when administered to man is not manifested. Caffeine, on the other hand, is a more potent cerebral stimulant, and when ingested superimposes volitional muscular activity over fatigue and thus increases one's capacity for muscular work. The evidence appears convincing that this action of caffeine is central and not peripheral.

Eichler (1938) tested caffeine on the performance of certain athletes assembled for the Olympics in Berlin (1936). In the 100 meter sprint, the runners receiving caffeine did not significantly improve their speed. In the high jump where muscular activity combines with mental precision in the performance, 63 per cent of the participants receiving caffeine improved their jump; 35 per cent did not. Here the difference is significant and supports the foregoing statements with regard to the site of the muscular action of caffeine.

**Absorption, fate, and excretion of caffeine.** Caffeine is readily absorbed from the gastrointestinal tract. Roth *et al.* (1944) showed that caffeine administered orally or intramuscularly to patients with peptic ulcer gave a sharp rise in acid secretion in the stomach. In fact, caffeine has been used to produce acid flow in a test meal. Coffee and tea with cream and sugar also elicit the flow of hydrochloric acid in the stomach (Roth *et al.*, 1944). It appears that coffee stimulates the flow of acid with or without caffeine.

Although caffeine increases the amount of acid, it is difficult to say with certainty that coffee is a prime factor in the pathogenesis of peptic ulcer; however, the evidence is clear that in hyperacidity with or without ulcer the beverage should be taken with moderation.

Caffeine is distributed to the various tissues of the body in approximate proportion to their water content. The compound passes readily into the central nervous system. Caffeine is nearly completely metabolized in man (Axelrod and Reichenthal, 1953). Only about 1 per cent is excreted in the urine. The rate of biotransformation of caffeine was found to be rather uniform from subject to subject. About 15 per cent is metabolized per hour. Using paper chromatographic procedure, Weinfeld and Christman (1953) observed that caffeine administered to human subjects was excreted in the urine as 1-methyluric acid. Evidence was suggestive that a small amount of 1,3-dimethyluric acid was also excreted. There appears to be no day to day accumulation of the drug in the tissues.

**Toxicity of caffeine.** Caffeine has an extraordinarily high margin of safety. The authors were unable to find any record of deaths resulting from overdosage. It has been estimated that 5 to 10 gm. may be fatal in man.

In the laboratory animals, excessive doses of caffeine produce convulsions. They are at first epileptiform. As the action descends to the cord, the convulsions become tonic and resemble those produced by strychnine.

The toxic manifestation of caffeine may be readily combated with the derivatives of barbituric acid such as amobarbital sodium.

**The caffeine-bearing beverages.** The drinks used by man which have stood the test of time are those which affect the central nervous system. The alcoholic beverages, tea, coffee, and the kola soft drinks fall in this class. Maté, a favorite South American drink, contains caffeine.

During 1962 the people of the United States consumed about 2.8 billion pounds of coffee, a per capita consumption of about 16 pounds. During the same year about 106 million pounds of tea were consumed, a per capita consumption of 0.60 pound.

The average cup of coffee contains a therapeutic dose of caffeine, 50 to 100 mg. Although tea contains more total methylated xanthines than coffee, less tea is used in the extraction process, and the beverage as a rule contains less caffeine.

Hawk, many years ago, examined 100 young men who were devoid of visceral disease. They were regular coffee drinkers. He found that they exhibited less satisfactory nervous reactions than those who did not drink coffee. Horst *et al.* (1936) observed that caffeine first improved the performance of target shooting and later disfavored it. These investigators gave 4 mg./kg. of caffeine to normal subjects. They observed a slight increase in oxygen consumption. From ½ to 1½ hours after the ingestion the pulse rate increased 8 to 9 per cent. The same individuals were given decaffeinized coffee, and the foregoing findings were not observed.

The question of the use of coffee and tea by individuals with different types of diseases is important. In gout coffee is often prohibited. Additional uric acid is not formed, but methylated uric acid does appear as a metabolite in the urine. It is doubtful whether this product in quantities in which it is formed aggravates the disease. Furthermore, the interdiction of coffee in azotemic nephritis does not seem justified as the small amount of nitrogenous waste formed by the biotransformation of caffeine in the body is insignificant.

In hypertension caffeine beverages are often denied. If the patient is not overly excited by coffee or tea, the denial of these drinks again does not appear to be warranted. Many tolerant coffee drinkers feel relaxed and tranquilized after their morning coffee. The direct effect on the cardiovascular system does not appear to warrant the removal of the drinks. On the other hand, mild indulgence might serve as a comfort and may relieve anxiety and mental depression that often accompany the disease.

In hyperacidity with or without peptic ulcer, if caffeine beverages are desired by the individual, tea is to be preferred to coffee. It contains less caffeine and does not contain the acid-stimulating volatile oils which are present in coffee. Excessively hot beverages should also be avoided.

In nervous insomnia coffee and tea are wisely interdicted. Decaffeinized coffee and very weak tea may be permitted. If the patient is being sedated with phenobarbital the repetitious use of coffee often makes it necessary to increase the dosage schedule of the sedative.

The over-indulgence in caffeine-bearing beverages, particularly coffee, in certain susceptible individuals gives rise to palpitation and tachycardia. Repetitious stimulation of the central nervous system produces vexation, fretfulness, and malaise. These may be accompanied by insomnia, all of which aggravate the circulatory symptoms. Premature systoles may be observed. The removal of caffeine-containing beverages from such an individual is desirable. Decaffeinized coffee will frequently serve the needs of the patient adequately.

**Diuresis and caffeine.** The effect of caffeine on urine flow is discussed under *Water Balance,* page 811.

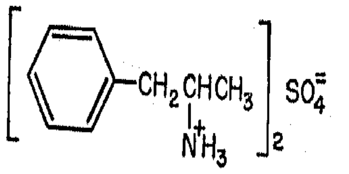
**The therapeutic uses of caffeine.**

1. The principal use of caffeine is to produce mild cerebral stimulation. For this purpose 0.2 gm. orally is generally sufficient.
2. Caffeine and sodium benzoate is employed parenterally as a respiratory stimulant. Its dose is 0.5 gm. For this purpose it is used to combat toxic depressions of sedative drugs and to support a failing respiration produced by organic disease.
3. Caffeine is used to relieve headache in combination with analgesics such as aspirin and acetophenetidin.

### AMPHETAMINE SULFATE, U.S.P.

Amphetamine was introduced under the name of Benzedrine as a drug suitable for administration by inhalation to produce shrinking of the nasal mucosa in head colds and sinusitis. It is a sympathomimetic amine and like epinephrine stimulates the effector cells of the sympathetic division of the autonomic nervous system. In addition, amphetamine was observed to elicit cerebral stimulation. This feature of its pharmacologic response will be discussed in this chapter. The autonomic action of the drug is considered under the sympathomimetic amines, page 554.

Amphetamine is 1-phenyl-2-aminopropane as shown in the accompanying formula. For inhalation purposes the free base or its carbonate was used. For cerebral stimulation the sulfate of the base is the salt of choice. The sulfate is a white, odorless powder. It is freely soluble in water.



$$\left[C_6H_5\text{-}CH_2\underset{\overset{|+}{NH_3}}{CH}CH_3\right]_2 SO_4^=$$

Amphetamine Sulfate, U.S.P.

**Respiratory action of amphetamine.** Alles (1933) made the observation that amphetamine produced an arousing action on animals under anesthesia. This prompted the use of the drug as a stimulant to the respiratory centers in cases of barbiturate intoxication. In depressed states amphetamine not only combats a failing respiration, but its pressor action restores the blood pressure to higher levels. The value of amphetamine as a respiratory stimulant is definitely established. For combating respiratory depression the drug is most effective when administered subcutaneously; 10 mg. of amphetamine sulfate in 1 to 2 ml. of distilled water is recommended. It may be repeated as necessary when the central nervous system and circulatory responses subside.

**Psychic stimulation and therapy with amphetamine.** Small doses of amphetamine that produce little effect upon the circulation or respiration when administered orally evoke definite stimulation of the sensory cortex. This is manifested by an increase in *mental alacrity, brighter spirits,* and a *mild euphoria.* The individual may experience restiveness, volubility, and insomnia.

The psychic stimulation produced by amphetamine in normal individuals is generally followed by a sense of depression and fatigue. The drug frequently superimposes an excitability over a fatigue, permitting the individual to engage temporarily in mental and physical activity with more zest. It does not obliterate the basic need of the body for rest.

In normal individuals the action of the drug has not proved itself capable of facilitating better mental performance. In fact with medical students in examinations, the authors' observations indicate that the nervousness frequently elicited by the drug is a distinct mental hazard. Knehr (1940) tested subjects by ability to perform mathematical problems with and without amphetamine. He concluded that with subjects working near their capacity, amphetamine did not appear to improve the scores in code or square root tests.

*In mild psychogenic depressive states,* however, amphetamine has proved to be of definite value. In convalescence, old age, grief, and various types of melancholia, the use of the drug is often indicated.

In *narcolepsy,* amphetamine has been especially useful. The drowsiness is abolished by amphetamine. For this purpose 5 mg. of the drug are given 3 to 4 times a day at first. The dosage schedule may be increased to 10 mg. four times daily. The drug should be avoided before bedtime. There is little evidence of tolerance being developed with the continued use of the drug.

One of the usual therapeutic uses of dextroamphetamine is in the treatment of behavior disorders in children. Bradley (1937 *et seq.*) found the drug to be most valuable in pediatric behavior disorders in which maladjustment was expressed in restlessness, noisiness, hyperactivity, and distractibility. Dextroamphetamine is effective in subduing the hyperkinetic state in a large segment of these children. It appears that often the effect of phenobarbital in the same type of disorder often aggravates the condition. There is no adequate explanation for the apparent paradoxical effects of the drugs in the treatment of hyperkinetic children.

**Untoward effects of amphetamine.** Amphetamine is contraindicated in hypertensive individuals or those with cardiovascular disease. In anxiety states, in hyperexcitability, and chronic insomnia the drug should be avoided. The repetitious use of the drug for a psychic "pick up" in normal persons is interdicted. The drug may become habit-forming. Cases of collapse have been recorded from the continual use of the drug in masquerading a fatigue with hyperexcitable states.

Continual dosage may give rise to hypertension, restiveness, vexation, and gastrointestinal disturbance. Overdosage may produce xerostomia, pupillary dilatation, precordial pain, palpitation, chills, and collapse.

The antidotes for amphetamine intoxication are sedatives such as the short-acting barbiturates.

**Dextroamphetamine Sulfate, U.S.P. (Dexedrine).** Amphetamine contains an asymmetric carbon atom and hence exists in *d* and *l* forms. The *d,l* variety (racemic form) is the form most generally used. Alles (1939) resolved the racemic compound into its *d* and *l* components and found that the *d* variety elicited a more powerful central action than either its *l*-isomer or the racemic form. The sulfate of this compound is available as *Dexedrine.*

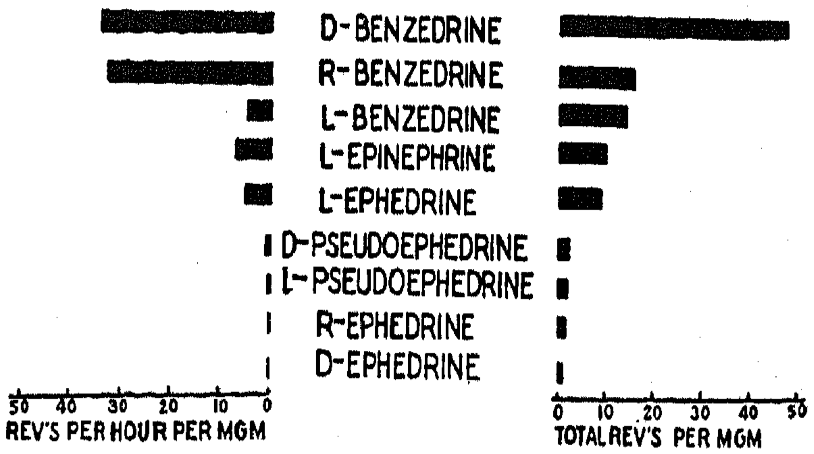
Schulte and his associates (1941) studied the stimulating activity of various sympathomimetic amines on the central nervous system of the rat.

TABLE 31-1

*Relative Central Stimulant Activity of the More Active Amines*

(Schulte et al., 1941)

The blocks on the left side indicate the maximal degree of stimulation produced by the most effective dose in mg./kg. of drug administered and the blocks on the right side, the greatest total stimulation per mg./kg. administered. The calculations were made from the averages of groups of 10 rats on each dose. Rev's indicate the degree of spontaneous activity.



They measured the summation of the activity of the animals after the subcutaneous injections of the various compounds. Their results are shown in table 31-1.

It will be observed from the table that *d*-benzedrine (*d*-amphetamine) or Dexedrine is the drug of choice for cerebral stimulation; amphetamine (*r*-benzedrine) is second. These results were confirmed in the main by Warren and Werner (1945).

Amphetamine was recommended in the treatment of obesity by Lesses and Myerson (1938). They found amphetamine to depress the appetite and increase the physical activity of their patients. Emerson and Abreu (1941) found irregular changes in basal metabolism when 20 mg. of amphetamine was administered orally to healthy individuals. The average increase was only 3.1 per cent of the basal level.

When used in obesity *d*-amphetamine is preferred to amphetamine because of its lesser activity on the peripheral nervous system and its stronger central action. The mechanism of the action of these drugs in diminishing appetite is not clearly understood. Several factors, however, seem to play an important role. *d*-Amphetamine tends to eliminate *anhedonia* which in some cases is responsible for nervous nibbling and unnecessary eating. The drug gives rise to brighter spirits and often concomitantly a more positive determination to adhere to a diet of lesser caloric intake.

Indeed, the action of *d*-amphetamine on the gastrointestinal tract appears to be slight. Sangster *et al.* (1948) carried out a most comprehensive study of the effect of *d*-amphetamine on gastric motility in the dog. They found that the parenteral administration of the drug usually depressed stomach contractions. The effect, however, was very transient and often did not occur at all when the dosage level was small. In man the literature reports are conflicting. There is probably a great deal of individual variation. It appears to be well established that the anti-appetite activity of the drug is due almost entirely to its central stimulating action. The action on the gastrointestinal tract is apparently an insignificant component of this action.

The experiments of Ahokas *et al.* (1950) demonstrated that amphetamine sulfate (10 mg.) is capable of producing simultaneously a decrease in acuity of sense of taste for sucrose and conversion of the sensation of appetite into one of satiety. It has been suggested that the anorexia produced by the drug is associated with its depressant action on the sense of taste for sucrose and its depressant effect upon olfaction.

The observation of Anokas *et al.* compares favorably with earlier work by Sangster *et al.* They found that *d*-amphetamine administered parenterally to dogs would convert a sense of hunger to one of satiety. This prevailed in the animal after denervation of the extrinsic nerves to the stomach and intestines. Such animals retained the characteristics of jealousy and selfishness. They would snatch food from the animals in neighboring cages and take it to their own, but

would not eat it. From data available it appears that *d*-amphetamine curbs the learned or conditioned aspects of one's desire for food, the *appetite*. This is a function of the higher cerebral centers. Hunger, however, which is an unconditioned, instinctive desire for food, likely controlled by hypothalamic centers, is not markedly affected by *d*-amphetamine.

It has been shown that the hypothalamus is the level of the brain most directly concerned with food intake (Brobeck, 1955). Two compensating mechanisms appear to operate. One is in the lateral regions and is concerned with eating—the *feeding center*. The other is in the medial hypothalamus and serves to inhibit the lateral mechanism. The medial mechanism is concerned with *satiety*. It is possible that these centers are influenced by many somatic processes, *viz.*, gastrointestinal movements, the composition of body fluids, and intermediate metabolism. Marrazzi and Hart (1955) demonstrated that *d*-amphetamine inhibited the synaptic transmission of impulses in the midbrain. It, therefore, appears more likely that the appetite-reducing action of *d*-amphetamine stems from blocking impulses reaching the feeding center in the lateral regions of the hypothalamus rather than by stimulating the medial hypothalamic center concerned with satiety. Stowe and Miller (1957) produced hyperphagia in rats by bilateral destruction of the ventromedial hypothalamic nucleus. In these animals *d*-amphetamine evokes a reduction of food intake. It was concluded that the effect of the drug was due to the blocking of impulses to the lateral feeding centers, since the medial satiety center was destroyed.

Edwards and Swyer (1950) in the University College Hospital of London, conducted a carefully controlled weight reduction experiment for 4 months on 24 patients. Their controls received a 1000-calorie-per-day food intake. Another group received this same food intake plus 5 mg. of *d*-amphetamine 3 times a day. A third group on the same caloric diet had 50 mg. of thyroid added 3 times a day. The patients receiving thyroid lost no more weight than the control group. Those with *d*-amphetamine showed a significantly greater weight loss than the control patients. Since the caloric intakes were the same, the questions of appetite and satiety were not involved in the experiment. These observers attribute the effect of *d*-amphetamine possibly to brighter spirits and a concomitant increase in energy expenditure.

The use of *d*-amphetamine should be permitted only under careful medical supervision. All of the precautions and contraindications of amphetamine hold with the use of this drug in obesity. In the treatment of obesity it is well to keep in mind always the fact that the human machine does not violate the law of the conservation of matter; namely, *in a chemical reaction there is neither loss nor gain in weight*. Excess weight must come from excessive food intake beyond the individual's energy output.

For obesity, 15 mg. to 20 mg. is given daily in tablets (5 mg. each). The first dose before breakfast, the next at 11 a.m., and the third dose at 4 p.m., the times of greatest hunger.

For cerebral stimulation in depressed mental states, *d*-amphetamine is given 5 mg. 3 times a day, avoiding a dose after the evening meal. When the condition is accompanied by malaise and restiveness, frequently the *d*-amphetamine is administered with amobarbital 32 mg. The mixture is known as *Dexamyl*. There are many clinicians who believe that this combination offers a distinct therapeutic advantage.

*d*-Desoxyephedrine (Methedrine, Pervitin) is also employed as a cerebral stimulant. It was used by the German Army in World War II to produce a prompt period of mental alacrity. This agent is official in the N.F. under the name of *Methamphetamine*.

**The central action of *d*-amphetamine.** In all cases where amphetamine has been used to produce central stimulation, it appears that *d*-amphetamine is more potent and produces fewer untoward effects. Indeed, *d*-amphetamine appears to have but one pharmacologic action in the recommended doses and that is of central stimulation.

The site of action of *d*-amphetamine on the brain is on the higher centers in the cerebral cortex. Maling and Acheson (1946), using decerebrate cats, showed that *d*-amphetamine antagonized the rigidity in the muscles of the neck and legs. It is believed that the action of the drug is mainly on the cortex. It appears that *d*-amphetamine enhances the inhibition mechanism in the motor cortex with a concomitant lowering of the threshold to stimuli from the alerting centers in the midbrain.

The most logical explanation of the cellular activity of *d*-amphetamine depends upon its capacity to inhibit the enzyme amine oxidase. This enzyme acts upon certain amines in the brain to form aldehydes which apparently depress tissue respiration. Mann and Quastel (1940) suggest that since *d*-amphetamine inhibits the amine oxidase it might reduce the quantity of aldehydes formed and thus permit an increase in tissue respiration. In this manner cerebral function may be accelerated. Since *d*-amphetamine is an inhibitor of amine oxidase, which is involved in the oxidation of norepinephrine, the sparing of norepinephrine for psychic stimulation is possibly one of the mechanisms of the action of the drug.

Tyler (1947) kept subjects awake for 112 hours by the application of repetitious stimuli. The experimental insomnia resulted in an increase in the rate in the potential changes in the brain far above the level during the control days. One of the actions of amphetamine sulfate is to increase the rate of electrical activity of the brain. During the experimental insomnia, amphetamine sulfate prevented the deterioration of performance tests within 48 hours. Tyler suggests that the action of amphetamine contributes an important condition required for remaining awake during experimental insomnia, namely, to increase the rate of electrical activity of the brain.

The question as to whether or not *d*-amphetamine can improve the performance of trained athletes has been investigated extensively by many workers. It is clear that the problem involves the administration of the drug, so called "pep pills," to participants in various competitive sports. The problem was critically studied by Smith and Beecher (1959). Their subjects were swimmers, runners, and weight throwers. They were given 14 mg./70 kg. of amphetamine adequately controlled by placebos in the double blind procedure. In each category of performance there was a significant improvement under the influence of the drug; the weight throwers showed the greatest improvement. Approximately 75 per cent of the trained athletes showed improvement in performance after amphetamine.

Karpovich (1959) studied athletic performance in 54 male students before and after 10 or 20 mg. of amphetamine. The test trials were made in running, swimming, and running to exhaustion on a treadmill. The drug had no effect (beneficial or deleterious) on 50 of the subjects. Of the 4 who were affected, 3 showed improved performance and 1 was deleteriously influenced.

Thus, the results of these 2 studies are contradictory. The results seem to indicate that the effect of amphetamine in athletic performance is unpredictable and very likely dependent on the mood of the athlete. That the weight throwers were affected most beneficially appears to have significance. Of the performance tests cited this one requires the greatest precision and judgment, coupled with the thrust of the weight. In this, elevation of the mood appears to be a factor, in the other tests mental alacrity is secondary to physical prowess and endurance. Amphetamine appears to act solely upon the brain. Other effects, if any, are sequential to this action. Similar findings were presented by Eichler (1938) with Olympic athletes in Berlin using caffeine. The drug benefited the high jumpers but not the runners.

Likewise, the effect of amphetamine on performance after experimental insomnia has been the subject of many studies.

Later work appears to be in conflict with the findings of Tyler. Kornetsky *et al.* (1959) subjected normal persons to a battery of psychological tests after 44 and 68 hours of sleep loss, with and without the simultaneous administration of *d*-amphetamine. Ten milligrams of the drug were given at 44 hours and 15 mg. at 68 hours. It was concluded that sleep loss produced a greater decrement in some performances than in others; measures of performance which reflect "lapses" seemed to be more affected than measures which were relatively insensitive to lapses. *d*-Amphetamine restored only the least impaired performances to the non-sleep deprived level; measures of performance sensitive to lapses still differed significantly from the non-sleep deprived level. These studies indicate that the effect of *d*-amphetamine in restoring to normalcy psychic deficits evoked by sleep deprivation is not marked.

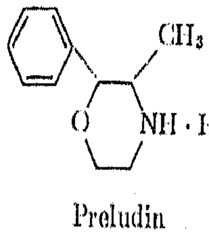
Kornetsky (1958) studied the effect of *d*-amphetamine on 8 subjects on their performance on a multiple stimulus-response apparatus. Simple motor behavior, choice reaction time, and learning were the procedures studied. Five or 15 mg. of *d*-amphetamine did not significantly affect motor coordination, reaction time, or learning, of the subjects.

As further suggestive evidence that the principal action of the amphetamine is upon the cerebrum, Lasagna and McCann (1957) showed that amphetamine was about 8 times more toxic to mice kept under crowded conditions than to those animals housed alone. Chlorpromazine, reserpine, and phenobarbital, but not pentobarbital, protected mice from the increased toxicity of amphetamine presumably agitated because of the crowded milieu.

**The fate of *d*-amphetamine.** *d*-Amphetamine is a rather stable compound. It is slowly oxidized or excreted by the body. The effect of a large dose may last 12 hours or longer. About one-half of the dose of the compound is metabolized, and the remainder is excreted in the urine unchanged. There appears to be no evidence that prolonged use will develop tolerance to *d*-amphetamine or modify its metabolic pathway.

### PHENMETRAZINE HYDROCHLORIDE (PRELUDIN)

There are numerous drugs available which are similar in structure and use to *d*-amphetamine to curb appetite and hence reduce body weight. These drugs are called *anorexigenic agents.* They are predominantly sympathomimetic amines. One of these compounds which appears effective and is extensively used is Preludin. Its structure is shown in the formula.



Preludin
Phenmetrazine Hydrochloride

Preludin is a white crystalline powder which is soluble in water. Like *d*-amphetamine, the principal pharmacologic response to Preludin is that of a mild stimulation of the psychic centers. It evokes mood elevation and curbs appetite. Its effect, in therapeutic doses on the cardiovascular system is negligible. However, its use in patients with severe hypertension, thyrotoxicosis, and acute coronary artery disease should be enjoined with caution.

**Clinical use of Preludin.** There are numerous reports on the clinical efficacy of Preludin in weight reduction. It appears to evoke a state of appetite appeasement with a lesser caloric intake. It is relatively free from side effects such as anxiety and insomnia. Xerostomia has been experienced in some patients.

Preludin has been used successfully in diabetics to evoke satiety on a low caloric intake (Robillard, 1957). Birnberg and Abitol (1958) used Preludin successfully to control weight during pregnancy. Fazekas *et al.* (1958) carried out a double blind study using *d*-amphetamine, Preludin, and a placebo. Their patients were mentally deficient. They observed a significantly greater degree of effectiveness in evoking satiety with Preludin than with *d*-amphetamine. Each was about 3 time more effective than the placebo. These investigators postulate a mechanism of action for Preludin similar to that discussed under *d*-amphetamine, page 477.

The dose of Preludin is 25 mg. 2 or 3 times daily. It is also available in 75-mg. prolonged action tablets for once a day administration.

**Other anorexigenic drugs.** Several additional drugs of the amphetamine series are used in curbing appetite. Their mechanism of action is believed to be similar to that of *d*-amphetamine. Their side effects, contraindications, and effectiveness also appear to be similar to those of *d*-amphetamine. Often patients will achieve therapeutic aims with one drug of the series better than with another. There is no crucial evidence, however, to indicate that *d*-amphetamine should not be the first drug of choice in this series.

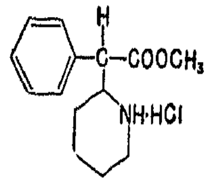
Among these anorexigenic agents are: *Diethylpropion hydrochloride* (*Tenuate, Tepanil*) *1-phenyl-2-diethylaminopropane hydrochloride;* Usual dose is 25 mg. 3 to 4 times daily; *Phentermine* (*Ionamin*) *α,α-dimethylphenethylamine,* this is a resin complex of the drug designed for sustained release. Usual dose is 15 to 30 mg. *Phentermine hydrochloride* (*Wilpo*) *α,α-dimethylphenethylamine hydrochloride;* usual is dose 8 mg. taken before mealtime.

### MERATRAN

Another compound used for psychic stimulation is α-(2-piperidyl) benzhydrol hydrochloride available under the name of Meratran. The therapeutic use of this cerebral stimulant has rapidly decreased. For a discussion of pipradol hydrochloride (Meratran) see the 5th edition, page 740.

### RITALIN

Ritalin is a newer central nervous system stimulant acting mainly upon the cerebral cortex. It is a piperidine derivative as shown in the following formula:



Methylphenidate Hydrochloride
Ritalin
(methyl α-phenyl-2-piperidineacetate
hydrochloride)

Ritalin occurs as a white crystalline powder which is freely soluble in water.

**Pharmacologic response to Ritalin.** The cerebral stimulation elicited by Ritalin is similar to the response evoked by caffeine and *d*-amphetamine. Monkeys receiving Ritalin reveal rapid brain activity in electroencephalographic tracings. Increased motor activity is also manifested.

In doses eliciting cerebral stimulation Ritalin produced no significant effect on blood pressure or respiration. Ritalin appears to increase the renal excretion of water. When injected into the renal artery of anesthetized dogs, Ritalin did not increase the renal blood flow.

The $LD_{50}$ of Ritalin upon oral administration to rats is 367 mg./kg. Prolonged feeding to rats of 5 and 10 mg./kg. daily showed no significant changes in blood picture, food consumption, or body weight gains. At autopsy after 3 months' feeding, the tissues of the principal viscera appeared normal grossly and histologically.

**Therapeutic use of Ritalin.** Mental sluggishness produced by the ingestion of phenobarbital was combatted by the simultaneous administration of Ritalin. In catatonic psychotic patients Ritalin was found to improve the mental status in 59 of 68 patients. The dose given was 10 to 40 mg. daily. Social appreciation and contact with reality were enhanced. Upon heavy dosage with reserpine in aggressive, overactive psychotic patients, Ritalin was shown to combat the accompanying drowsiness. The action of Ritalin as a drug to lift the mood of the patient and to combat depression produced by cerebral depressants appears to be established.

Ayd (1957) used Ritalin in 130 patients who exhibited various types of mental depression. He found it useful in relieving the depression of reserpine or chlorpromazine therapy. It served mainly as a mild psychic stimulant, and Ayd found it of little value in the treatment of "uncomplicated depressions."

Ferguson and Funderburk (1956) employed Ritalin along with reserpine in an effort to improve senile behavior. The tests included 215 hospitalized patients 60 years of age or older. Abnormal behavior, presumably owing to senility, was reduced in 171 cases and unaffected in 44. Not any of the patients with abnormal physical findings was worsened during approximately 1 year of treatment. Thus, Ritalin apparently is capable of combating the depressing action of reserpine and other drugs which elicit central nervous system depression as a component of their actions. The tranquilizing or calmative effect of such drugs is apparently not markedly altered by the simultaneous administration of Ritalin. These findings were confirmed by Wodraska *et al.* (1958) in 220 psychotic patients. The combination of reserpine and Ritalin provided a wider range of therapy with more gratifying results and a reduction in the degree and number of adverse side effects.

Ritalin effectively combats excessive barbiturate depression and severe depressed states evoked by many of the tranquilizing drugs such as chlorpromazine. For this purpose the drug may be given intravenously in doses from 30 to 50 mg. repeated in 30 minutes if necessary. Ritalin will also hasten the recovery time following barbiturate anesthesia. Gale (1959) found Ritalin useful in reducing depression of the newborn infant (1 mg./5 pounds of body weight intramuscularly) when administered to the mother before delivery or directly to the depressed infant. He found the procedure safe and effective and without serious side effects.

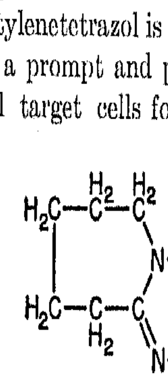
Ritalin has been found to be quite inactive as an inhibitor of amine oxidase. Maxwell *et al.* (1959) produced indirect evidence to show that Ritalin did not produce a generalized release of endogenous catecholamines from their depot sites. The basis for its action as a cerebral stimulant awaits further investigation.

Under the name of *Plimasin*, Ritalin is available mixed with Pyribenzamine to treat allergic conditions and avoid the sedative effects of Pyribenzamine. Plimasin tablets contain 5 mg. of Ritalin and 25 mg. of Pyribenzamine.

## PENTYLENETETRAZOL, N.F. (METRAZOL)

Pentylenetetrazol is a potent stimulant to the central nervous system. It has the structure shown in the accompanying formula. Pentylenetetrazol occurs in white crystals which are freely soluble in water.

**The response of the central nervous system to pentylenetetrazol.** The primary site of action of pentylenetetrazol is the central nervous system. It is a prompt and powerful stimulant. The principal target cells for pentylenetetrazol are those in the medulla and midbrain. In larger doses its action ascends to the cerebral cortex and descends to the spinal cord. The action of the drug appears to be one of direct stimulation and not reflexly through the carotid body.



Pentylenetetrazol, N.F.
Metrazol

Although the action of pentylenetetrazol in the medulla affects vasomotor and vagal centers as well as the centers of respiration, the principal use of pentylenetetrazol is to stimulate a failing respiration.

**Control of respiration and response to pentylenetetrazol.** Physiologists postulate that the following centers in the brain are concerned with the respiration. The medulla oblongata is the locus of the inspiratory and expiratory centers. The inspiratory center is likely the apneustic center. The upper pons contains the pneumotaxic center, and the cortex (frontal lobes) contains the control mechanisms for acceleration or inhibition of the lower centers.

The rate and depth of respiration is affected by peripheral chemoreceptors that react to changes in the oxygen-carbon dioxide tension and pH of the blood. One of these is the *glomus pulmonale* located in the wall of the pulmonary artery. The structure microscopically is identical with that of the carotid and aortic bodies (Krahl, 1960). Armstrong *et al.* 1961 demonstrated the sensitivity of the structure to the $P_{O_2}$ $P_{CO_2}$, and pH of blood, reflexly affecting respiration.

Furthermore, it has been shown that the chemosensitive portion of the respiration center is located on the anterior (ventrolateral) surface of the medulla and is in direct contact with the cerebrospinal fluid. Alterations in the pH of the fluid provide stimulation to the center and thus control the respiration. Mitchell, *et al.* (1963) suggests that one of the principal functions of the center is to maintain a constant pH of the cerebrospinal fluid, which serves as the chemical and biological environment of the brain. Evidence appears to be increasing that the control of respiration directly or reflexly is mediated through oxygen-carbon dioxide and pH changes in the blood.

Pentylenetetrazol stimulates directly the central respiratory mechanism, exerting its principal action in the medulla. It increases the depth of respiration and to a lesser extent the rate of respiration. It aids in reestablishing deep and regular respiratory movements. It facilitates better gaseous exchange in the lungs. Although there is some evidence to indicate that the centers are made more sensitive to carbon dioxide by pentylenetetrazol, this has not been definitely established.

Preston's work (1955) on the isolated segment of the cat's cerebral cortex with pentylenetetrazol indicated that as a convulsive drug the action was cortical and also equally effective at subcortical levels.

**Circulatory effects of pentylenetetrazol.** Pentylenetetrazol has been reputed to be useful in supporting a failing circulation in chronic circulatory insufficiency.

The evidence is not convincing to show that pentylenetetrazol exerts any direct value in this capacity. However, in respiratory depression involving the circulation, the circulatory improvement which may occur is likely the result of the improvement in respiration and the combating of cerebral and peripheral hypoxia.

Woodbury and his associates (1941) studied the blood pressure changes in dogs and man after pentylenetetrazol injections. They found that in man convulsant doses of pentylemetetrazol raised the arterial pressure on the average of 100 mm. of mercury. Vasoconstriction appeared to play only a minor role. The principal effect on blood pressure was due to contractions of skeletal muscle. The rise in pressure was limited to the period of the convulsive activity of the drug. The convulsive contractions markedly increased the extravascular pressure in most body areas. The compressed blood vessels responded by showing increased arterial pressure. There is, however, no effective increased pressure to the vital areas such as the brain, heart, and viscera. The blood vessels of these areas do not share in the stress of the extravascular pressure in skeletal muscle.

**Absorption, fate, and excretion of pentylenetetrazol.** Pentylenetetrazol is very rapidly absorbed when ingested or administered parenterally. The findings of Hildebrandt (1936) showed that the subcutaneous convulsive dose of pentylenetetrazol was 3 times its intravenous convulsive dose. This seems to indicate detoxification in the body. Tatum and Kozelka (1941), using cats, and Dille and Seeberg (1940), using rabbits, showed that pentylenetetrazol was detoxified in these animals and not excreted as such. The liver played the dominant role in the detoxification process.

**Effect of repeated pentylenetetrazol convulsions.** Whitehead and his associates (1940) gave dogs and rabbits repeated convulsive doses of pentylenetetrazol. They found organic lesions were produced. The principal site of damage was the cerebral cortex. Necrosis of the nervous parenchyma was observed in small circumscribed areas. This was occasionally associated with slight glial reaction and with diffuse degenerative change of moderate degree in the nerve cells. There were kidney and lung lesions found also. These workers believe that the pathogenesis of the lesions is the vascular spasm with its accompanying hypoxia rather than any direct effect of the drug. Masuoka (1958) showed that cats subjected to pentylenetetrazol convulsions exhibited about a 2-fold increase in lactic and pyruvic acids in the blood. The levels of the 2 acids returned to normal in about 2 hours. When the convulsion was blocked by succinylcholine, blood levels of lactic and pyruvic acid did not increase upon the injection of pentylenetetrazol.

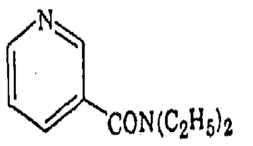
**The therapeutic uses and dose of pentylenetetrazol.**

1. The principal therapeutic use of pentylenetetrazol is as a *respiratory stimulant in emergencies.* These include depression from barbiturates, anesthetics, and alcohol, and cases of near drowning.
2. Although there are numerous other conditions such as fatigue states, senility, arteriosclerosis and bronchial asthma in which pentylenetetrazol has been used, its value in these conditions remains to be established.

Pentylenetetrazol is supplied in ampules (10 per cent solution) 1 and 3 ml. Each ml. contains 100 mg. of drug. The drug is given intramuscularly, subcutaneously, or intravenously, 1 to 3 ml. Pentylenetetrazol tablets; 100 mg. are also available.

### NIKETHAMIDE, N.F. (CORAMINE)

Nikethamide or Coramine is a synthetic pyridine derivative. The formulas show its constitution and relation to nicotinic acid. Nikethamide is a clear, colorless or pale yellow liquid. It has a characteristic aromatic odor. It is miscible in all proportions with water.



Nikethamide, N.F.
(N,N-diethylnicotinamide)

**The response of the central nervous system to nikethamide.** The action of nikethamide is principally on the central nervous system. It is a prompt and powerful central nervous system stimulant. On the central nervous system the target cells in the nikethamide action are mainly in the medulla, although in larger doses the action of the drug ascends to the cerebral cortex and descends to the cord. Large doses produce convulsions.

The principal stimulation of nikethamide in on the medullary centers. The vagal and vasoconstrictor centers are stimulated, but the predominating action is on the centers of respiration. These are not stimulated by direct central action as with pentylenetetrazol but reflexly through action on the carotid body. Peters *et al.* (1959) injected nikethamide into the salamander in which the cerebral cortex is lacking. Tonic seizures were evoked which likely involved the action of the drug on the brain indicating that the cerebral cortex is not primarily involved in the action of nikethamide.

Various stimuli to the respiratory mechanism act in different ways. Thus, decreased oxygen supply stimulates the respiration reflexly. Increased carbon dioxide supply stimulates the respiration through the direct and reflex mechanisms, as does also a decreased blood pH. Drugs like cyanide, lobeline, and nikethamide exert their actions directly and through the carotid body. The chemoreceptors of the carotid body are the last to succumb to adverse conditions such as hypoxia. They are undifferentiated tissue of embryonic origin and hence are more resistant to unfavorable circumstances than the highly specialized cells of the medulla. Through the action of drugs on the carotid body intense respiratory stimulation can be achieved. This sometimes prevails when the direct medullary action is no longer effective.

**The circulatory effects of nikethamide.** In laboratory animals, nikethamide produces an increase in blood pressure which is preceded by a transient fall. The circulatory effect appears to be secondary to the improvement of the respiratory mechanism. Small doses of the drug do not affect coronary flow. Large doses increase the flow of blood through coronary vessels. The value of the drug in the production of increased coronary flow in therapeutics has not been established.

**Absorption and fate of nikethamide.** Nikethamide is readily absorbed from the various avenues of administration. The most effective manner of giving the drug is by intravenous injection of the 25 per cent aqueous solution. In the body, nikethamide is normally converted to nicotinamide and excreted as nicotinamide methochloride (Coulson and Stewart, 1946).

**The therapeutic uses and dosage of nikethamide.**

1. The principal therapeutic use of nikethamide is as a *respiratory stimulant in emergencies.* It is used in depression caused by barbiturates and alcohol, and in threatened anesthetic collapse.
2. Nikethamide exhibits antipellagrous activity.

The drug is available in 25 per cent W/V solution (ampule 1.5 ml.) for parenteral use. The best results are obtained in respiratory emergencies by its intravenous use. The dose is 1.5 to 3 ml. to be repeated when necessary.

**Bemegride (Megimide)** is a cerebral stimulant that has been used mainly in barbiturate poisoning. Chemically it is $\beta,\beta$-ethylmethylglutarimide. The activity of Megimide against barbiturate intoxication has been demonstrated. It has had extensive trials by many investigators in various clinics as a barbiturate antagonist. Megimide exerts a striking stimulating effect on the respiration and reflex activity. Louw and Sonne (1956) consider that it is a valuable agent "to bring patients into a stabilized physiological state." However, in their series of barbiturate intoxications, Megimide was not capable of increasing the rate of barbiturate elimination or influencing the blood level of barbiturate on awakening or shortening the duration of coma. They do not believe that Megimide enters into competitive inhibition with the barbiturates as does N-allylmorphine with morphine. Its action appears to be limited to its analeptic properties. Zapata-Artiz *et al.* (1959) studied the action of Megimide in mice, rabbits, and dogs with respect to antagonism to barbiturates and other hypnotics. They concluded that Megimide was a convulsive drug similar to pentylenetetrazol and not a specific barbiturate antagonist, since its activity was exhibited against depressed states caused by structurally unrelated hypnotics. Their data indicate no advantage shown by Megimide over pentylenetetrazol. On the other hand, Matts (1959) is of the opinion that the mode of action of Megimide in barbiturate poisoning is "partly by functional barbiturate antagonism and partly by an analeptic effect." It appears that evidence for specificity of antagonism between Megimide and the barbiturates rests on an insecure basis.

There are complications caused by an overdosage of Megimide such as mental disturbances similar to those induced by the hallucinogenic drugs. Kjaer-Larsen (1956) observed acute psychotic states prevailing in 15 of 50 patients appearing 1 to 4 days after recovery from severe barbiturate intoxication after treatment with Megimide. He is of the opinion that the barbiturate intoxication rather than Megimide was responsible for the mental disturbance. In his series of treatments convulsive seizures were encountered in 15 cases. Mild convulsive seizures are not uncommon. Convulsions produced in some instances have been sufficiently violent to cause vomiting with the aspiration of the gastric contents. Louw and Sonne (1956) point out, however, that as a central nervous system stimulant Megimide has unusual properties. Among these are that it does not elevate the blood pressure or induce hyperpyrexia as do the commonly used analeptics. They consider Megimide a valuable supplement to other agents used in narcotic intoxications.

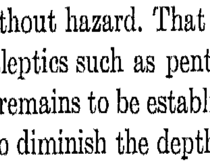
Cass (1956) found that Megimide was capable of reversing the EEG pattern of deep depression elicited by all barbiturates and thiobarbiturates tested. In this respect it appeared to be more effective than other analeptics.

Megimide is administered intravenously in concentrations of 500 mg. in 100 ml. of normal salt solution. The maximal dose at any given time is 1500 mg. The solution is infused at a rate of about 1 drop per second. Follow-up doses may be used, dependent upon the patient's needs.

From the available data it is clear that Megimide is not indicated in cases of barbiturate poisoning which are mild or moderately severe as described on page 407. In very severe cases it may prove of value but not as a substitute for other supportive measures previously mentioned. Its use is not without hazard. That it is superior to the older analeptics such as pentylenetetrazol or nikethamide remains to be established. Megimide is also used to diminish the depth of thiobarbiturate anesthesia when this is desirable and also to hasten recovery.

### ETHAMIVAN (EMIVAN)

Ethamivan is a central nervous system stimulant used primarily for the purpose of arousal from anesthesia and hypnotic intoxication. Chemically it is the diethylamide of vanillic acid as shown in the formula.



Ethamivan
Emivan

Ethamivan is a white crystalline powder that is sparingly soluble in water.

**Pharmacologic response to ethamivan.** Miller *et al.* (1962) showed that ethamivan evoked a strong stimulating action on the central nervous system in laboratory animals. It appeared from the studies that the action was mainly on the carotid (and possibly the aortic chemoreceptors). It likely also stimulates the central chemoreceptors. The effects on the circulatory system appear to be negligible (Avinger *et al.* 1952). Ethamivan enjoys a wide margin of safety.

**Clinical use of ethamivan.** The drug is used primarily for the purpose of arousal from hypnotic depression and anesthesia. For this purpose it is used intravenously in a 5 per cent solution. Silipo *et al.* (1961) used ethamivan in 43 patients with respiratory depression resulting from barbiturate intoxication and in patients with severe pulmonary emphysema. He reported good results in most cases with minimal side effects. The side effects were *pruritis, muscular twitching, sneezing,* and *excitation.*

In respiratory failure 1000 mg. of the drug is administered intravenously in 250 ml. of 5 per cent dextrose solution. The rate is 7.5 to 10 mg./min. Ethamivan is also available in tablets for oral administration 20 to 60 mg. 2 to 4 times daily.

### STRYCHNINE SULFATE, N.F.

Strychnine sulfate is the sulfate of an alkaloid obtained from the ripe seed of *Strychnos nux vomica.* The nux vomica seed or "button" contains about 1.25 per cent of strychnine. It contains also another alkaloid of far lesser pharmacologic potency known as *brucine.*

**Nux vomica.** The 10 per cent tincture of nux vomica has been used for years as a "tonic." It is also used as a simple bitters. The tonic value of the preparation rests on an insecure scientific basis. There is no doubt about the bitterness of the tincture. However, gentian and bitter orange peel can evoke a bitter taste, if desirable, and these drugs are not toxic. This preparation therefore in our opinion has passed beyond the realm of rational therapeutics.

**Strychnine sulfate.** This is a white, crystalline soluble salt eliciting a very bitter taste even in high dilutions (1:700,000). It is a powerful stimulant to the spinal cord. The stimulating action in large doses extends to the medulla. It is a convulsive poison.

Like nux vomica, strychnine has been used as a tonic, simple bitters and in amblyopia, in incontinence of urine, in asthenia, in paralysis, and many other conditions. There is no crucial evidence to show that strychnine is useful in any of these or other conditions in which it is used. Therefore, the authors hold the view that strychnine, like its parent drug nux vomica, no longer holds a rational place in the physician's armamentarium.

**The action of strychnine on the cord.** Strychnine is employed extensively as a poison for rodents, and clinical cases of strychnine poisoning are sometimes seen. Furthermore, the action of strychnine on the spinal cord has been of intense physiologic interest. Therefore, the locus and mechanism of the action of the drug will be given consideration. The following points are of interest.

1. If strychnine is injected into one of the lymph sacs of a frog, when absorption occurs the animal shows a rapid series of tonic convulsive seizures. The hind legs are strongly extended, and the body is arched backward (opisthotonus).

2. Claude Bernard exposed one of the sciatic nerves of a frog and tied a ligature around the gastrocnemius muscle excluding the nerve. He then injected strychnine into the muscle peripheral to the ligature. No tetanus occurred in the operated leg, and hyperreflexia was not produced. When strychnine was injected into the other leg and absorbed, hyperreflexia occurred, and tetanus was present in both legs. Therefore strychnine does not act directly on motor nerve endings, nor on the myoneural junction. Furthermore, it does not act directly on skeletal muscle.

3. If one removes the heart from a frog, decerebrates the animal, and paints strychnine solution on the cord, the hyperflexia is evoked. This, therefore, is direct evidence that the locus of the action is the spinal cord.

4. Later, experimenters Owen and Sherrington (1911) and de Barenne (1933) established the site of the action of strychnine in the cord. The latter investigator lifted the lumbrosacral cord of a cat by severing the denticular ligaments and painted a solution of strychnine (colored with toluidine blue) on the ventral surface. The animal showed twitchings and muscle contractions, but no frank convulsive seizures. The dorsal surface of the cord was strychninized in a similar manner in the same segments. Definite tetanus ensued.

It was concluded, therefore, that for the convulsive seizures characteristic of strychnine to occur, the perikarya of the dorsal horns of the spinal cord must be poisoned simultaneously with the cell bodies of the motor nerves in the ventral gray matter.

The action of strychnine on the spinal cord emphasizes the physiologic dictum that every afferent neuron in the central nervous system has a potential connection with every efferent neuron. Strychnine makes these potential connections real.

**Further studies on strychnine action.** Nachmansohn (1938) showed that strychnine rapidly inactivated cholinesterase. It was his opinion that the hyperreflexia produced by strychnine by its action on the cord was due to its action on this esterase, which in turn gives rise to a freer play of the motor-stimulating response of acetylcholine.

It is of interest that even after a terminal strychnine convulsion has persisted for a half hour the cord shows no significant change other than a mild hyperemia. No anatomic damage is done, which fact lends support to the Nachmansohn hypothesis, suggesting that a biochemical "lesion" is responsible for the action. Strychnine behaves typically like a lipid-soluble antagonist of cholinesterase, which prevents the destruction of acetylcholine within the nerve cells and should thus behave as a convulsant stimulant.

Adamson and Fouts (1959) studied the metabolism of strychnine by the livers of several species of laboratory animals. The degradation was accomplished by the microsomes with the soluble fraction supplying the cofactor. Maximal metabolism required reduced TPN, oxygen, a pH of 8.4, and a high concentration of strychnine. The nature of the metabolite or metabolites was not established; the metabolic processes, however, destroyed the pharmacologic activity of the strychnine molecule.

**Strychnine poisoning in man.** Cases of poisoning with strychnine are becoming less common. They arise from the purposeful use of the drug with homicidal or suicidal intent. The drug is used as a rodent poison and may inadvertently be taken. Pills of strychnine used in the home by elderly people as a "tonic" may be swallowed by children; they are small and often sugar coated. Besides, there are still laxative pills used containing strychnine, such as the *pills of aloin, strychnine,* and *belladonna.* A severely constipated individual may poison himself by the use of several of these pills. Each pill contains 1 mg. strychnine sulfate.

Strychnine is readily absorbed from the gastrointestinal tract, and in large doses symptoms of intoxication occur within a matter of minutes. There is a case on record of a woman dying from 5 mg. of strychnine and a man recovering after taking 1 gm. From 60 to 90 mg. is likely to be fatal.

The strychninized individual develops a cold sweat; there are fibrillary twitchings of the hands and feet. The convulsive seizures then ensue, sometimes with an involuntary cry. The opisthotonus may be so severe as to permit only the heels and head to rest on a flat surface. The tonic convulsions later become clonic. They may persist for 10 minutes or last for several hours. Pain is excruciating and consciousness is maintained until death. This distinguishes the pharmacologic syndrome of strychnine poisoning from grand mal seizures of epilepsy.

Death occurs from respiratory arrest. Travell and Gold (1935) suggest that the arrest is primarily due to fatigue of the respiratory centers by excessive bombardment from the periphery which are normally subthreshold. Abreu and Woodbury (1943) studied the effects of convulsive doses of strychnine on normal and anesthetized dogs. They were able to make blood pressure readings with the Hamilton-Woodbury hypodermic manometer. They state, "Anoxemia and hyperacidemia may be more important factors than fatigue by bombardment with sensory impulses in causing fatal respiratory center paralysis during strychnine convulsions." They found the blood pressure to rise from extravascular pressure during the convulsive syndrome.

Asphyxia appears to be the principal factor in producing the terminal respiratory failure following strychnine convulsions. The great oxygen demand from skeletal muscle activity, terror, and a failing circulation likely contribute to the exodus.

In death the patient is said to be found with his legs in extensor rigidity. The arms may be extended or flexed over the chest. There is a derisive grin on the face (*risus sardonicus*). The facial expression is not always characteristic.

**Treatment of strychnine poisoning.**

1. Gastric lavage, claret-colored potassium permanganate solution.
2. Keep patient warm, quiet, in dark, free from noise.
3. Barbituric acid derivatives.
   Sterile solution of amobarbital sodium may be cautiously injected intravenously, 0.25 gm. in 2.5 ml. of sterile distilled water.
4. Inhalation of volatile anesthetics is useful—ether.

The hyperreflexia of strychnine is antagonized by the depressant action of amobarbital and ether.

### PICROTOXIN, N.F.

Picrotoxin is an active principle obtained from the seed *Anamirta cocculus*. It is a respiratory stimulant and convulsive. It was used formerly in the treatment of barbiturate intoxication. For a description of its use see 5th edition, page 747.

### LOBELINE

Alpha-lobeline is the principal alkaloid of *Lobelia inflata* (Indian tobacco). This alkaloid has been used for emergency stimulation of the respiration. Its action resembles that of nicotine (Edmunds, 1904). Its action is unreliable, and effective doses are not safe (Norris and Weiss, 1927).

### AROMATIC AMMONIA SPIRIT, SMELLING SALTS, AND BRANDY

The reflex stimulating action of ammonia and ammonium carbonate (which emits the odor of ammonia) is discussed on page 202. The reflex stimulating action of brandy and distilled alcoholic beverages is discussed on page 280.

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# 32

# *The Use of Drugs in the Treatment of the Mentally Ill*

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Mental illness and its treatment are major problems of society. To emphasize the scope of mental disease one needs only state that the plurality of the hospital beds in the United States are occupied by mentally ill patients. In this country about one million patients are treated each year in public and private mental hospitals. According to United States Public Health Service studies, the cost of caring for these people is over a billion dollars a year. The Joint Commission on Mental Illness and Health has estimated that the total direct and indirect cost of mental illness, including the economic loss of productivity and income, is in excess of 3 billion dollars yearly.

Fortunately, the nature of mental illness is such that a large number of patients are released from mental hospitals within the first year. However, it is also characteristic of the disease that relapse occurs and many patients return to mental hospitals. A discouragingly small number of patients leave mental institutions after more than a year of hospitalization; others remain in mental hospitals for many years.

Progress in the treatment of the mentally ill with drugs has lagged behind the rapid advances made in other fields of medicine such as in the treatment of infectious diseases and endocrine disorders. Fortunately, within the last decade definitive advances have been achieved and serve to point out first, that the problem is not an insurmountable one, and second, that mental disturbances treated with drugs of certain chemical configurations may elucidate some of the baffling functional brain changes in mental illnesses.

**Types of cerebral disturbances and drug responses.** In the relatively minor mental disorders, such as the *psychoneuroses*, sedative drugs have played an important role in the psychiatric management of the patient. For example, the widespread use of phenobarbital in general nervousness, anxiety states, and hysteria is a well-established application of drug therapy in these potentially modifiable emotional states. In the paroxysmal cerebral dysrhythmia of epilepsy, striking advances have been made in drug therapy, and many new drugs are available to treat these convulsive disorders.

It is only, however, in very recent years that the major forms of mental illness, the psychoses, have shown definite improvement with drug therapy. The first drugs used successfully in these conditions were chlorpromazine and the alkaloid reserpine. Today there are many psychopharmacologic agents available with many others undergoing clinical trial. Indeed, in mental institutions the use of these drugs has revolutionized the handling of mentally disturbed patients (Ayd, 1963).

**Biochemical basis of psychopharmacology.** Thudicum, the founder of modern neurochemistry, apparently was the first to advance the concept of a biochemical basis of mental illness. Interest in this approach to an understanding of normal and abnormal brain function has been intensified by the discovery of specific chemicals that cause psychotic-like effects in man and the antipsychotic virtues of a number of drugs. The almost simultaneous reports of the remarkable effects of minute amounts of lysergic acid diethylamide accidently discovered by Albert Hofmann, and the effects of chlorpromazine and reserpine in tranquilizing states of agitation and anxiety in mental illness, were two factors that catalyzed the explosive growth of psychopharmacology since 1954. These discoveries strongly suggested that there may be a biochemical basis for such diseases as schizophrenia and the psychotic depressions. Reinforced by the dramatic disclosure of the usefulness of drugs in mental illness, many laboratories are now focusing their attention on the chemistry of the brain and how this may be related to psychiatric states and drug effectiveness.

The accumulated knowledge of brain metabolism, and the influence of drugs and chemicals upon behavior, electrical activity, and biochemical changes within the central nervous system, would constitute a respectable volume. Several pertinent references to reviews of this subject are cited, and some of the current concepts will be briefly alluded to in the discussions of the pharmacology of the individual drugs. No unifying concept has emerged that offers a satisfactory understanding of the basis of psychopharmacology.

The oxygen consumption of brain tissue is very high; under basal conditions it may amount to 25 per cent of the entire oxygen uptake of the body (Kety, *et al.*, 1948 *et seq.*). The intense metabolic functioning of the brain is shown by the fact that in the waking state the temperature of the brain is 0.5°C. higher than that of arterial blood. Gray matter, per unit weight of tissue, consumes 4 times the amount of oxygen utilized by white matter. Glucose is the major fuel of the brain. Other substances such as *l*-glutamic acid, amines, and certain fatty acids are utilized by the brain but only in relatively small amounts. Thus, it appears for normal cerebral function the availability of oxygen and the utilization of glucose and its metabolites are the prime factors. Drugs that interfere with this metabolic pattern modify cerebral function. Agents that diminish oxidative phosphorylation, such as certain barbiturates, produce depression of cerebral metabolism and sleep or anesthesia. Nevertheless, the problem is not a simple one, for certain agents such as chloral hydrate do not interfere with oxidative phosphorylation and yet do serve as hypnotics.

It appears therefore that decreased activity or stimulation of cerebral functions has not as yet been reduced to the simple matter of glucose metabolism. Therefore, the complex problem of consciousness, and its variants, appears exceedingly obscure when considered at a cellular level with regard to drug action. Certain strides, however, have been made in recent years in an attempt to tackle this intricate problem. It is a matter of common knowledge that many drugs so interfere with cerebral function as to produce thinking disturbances. Alcohol and morphine are examples which, however, structurally have little in common. A number of chemical substances of known composition produce abnormal behavioral effects in animals and hallucinations, disorientation, and psychotic-like symptoms in man. The discovery of the psychotic-like effects of D-lysergic acid diethylamide provided a stimulus for further explorations, for it was postulated that the endogenous production of a similar substance might be involved in mental aberrations.

**D-Lysergic acid diethylamide (LSD-25, Delysid).** D-Lysergic acid constitutes the essential portion of the structure of ergonovine, one of the principal alkaloids of ergot. It has long been recognized that it was the ingestion of ergotized rye that produced the epidemics of *ergotism*, in which thinking disturbances were one of the symptoms.

In 1943 the chemist Albert Hofmann, while working with derivatives of lysergic acid, including D-lysergic acid diethylamide, experienced vertigo and blurring of mental alacrity. He checked his observations by ingesting 0.25 mg. of the compound and again found himself beset by a syndrome of hallucinations, depersonalization, and vertigo. Hofmann recorded his experience in the following paragraph.

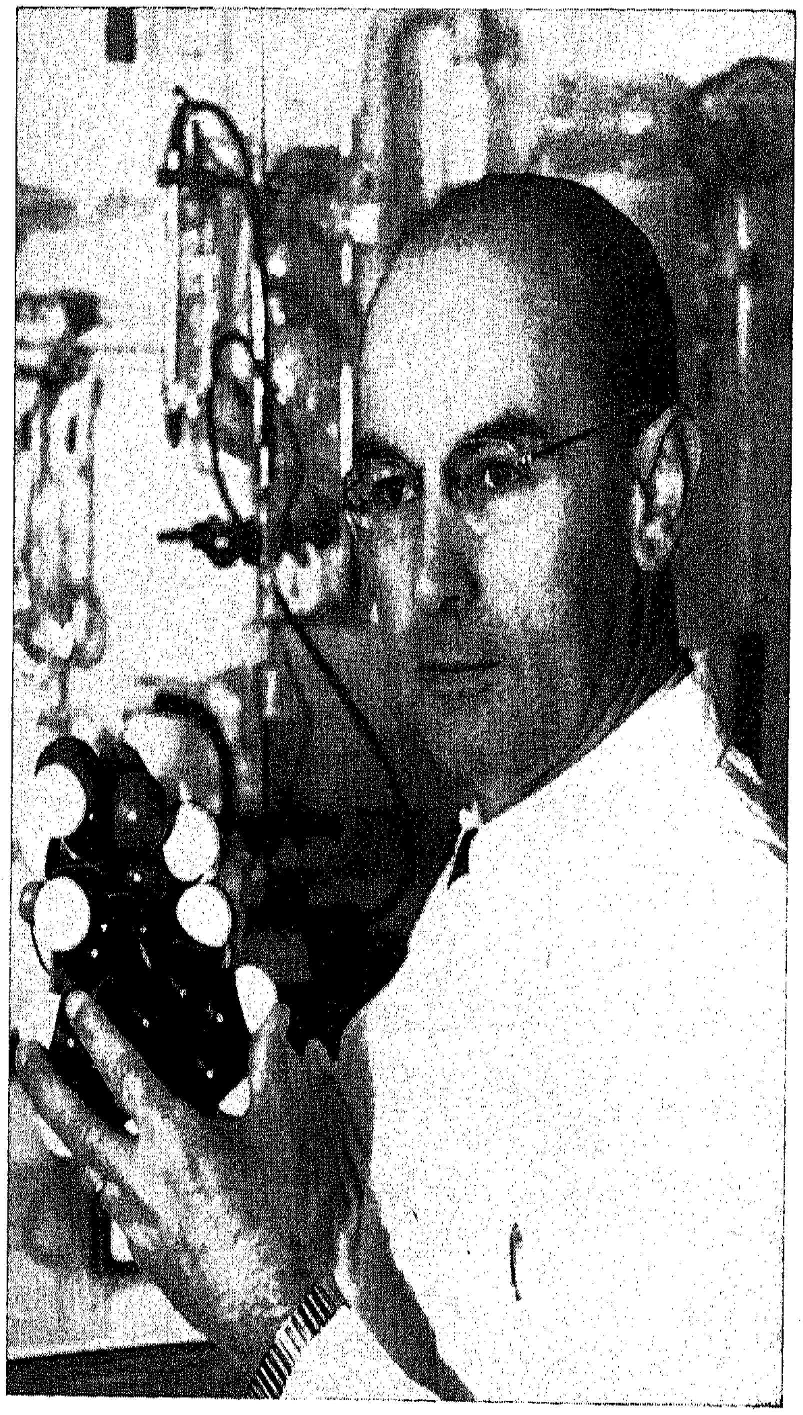
> "Last Friday, April 16th, I was forced to stop my laboratory work in the middle of the afternoon and to go home, as I was overcome by a peculiar restlessness associated with mild dizziness. Having reached home, I lay down and sank into a kind of delirium which was not unpleasant and which was characterized by extreme activity of the imagination. As I lay in a dazed condition with my eyes closed (I experienced day light as disagreeably bright), there surged in upon me an uninterrupted stream of phantastic images of extraordinary vividness and accompanied by an intense, kaleidoscope-like play of colours. The condition gradually passed off after about two hours."

Since this striking observation by Hofmann, many investigators have confirmed his findings. Volunteers who have taken the drug experience a mental intoxication which has features common with the thinking disturbances of schizophrenia and paranoia. In the experimental psychoses produced by D-lysergic acid diethylamide tartrate (LSD-25) persons can describe their symptoms and yet retain a knowledge that they are drug induced. Contact with reality is not lost. The amazing feature of the action of LSD-25 is its potency. In this respect it vies with certain of the vitamins and hormones. The administration of as little as 1 mcg./kg. will elicit the hallucinogenic effect.

For centuries man has used various types of hallucinogens as euphoriants. These include native plants, cacti, and mushrooms (Hofmann, 1961; Himwich *et al.*, 1961; Carr, 1959). It is of interest that LSD-25 is the most potent compound that has been obtained.

LSD-25 appears to block cortical inhibitions. There are likely specific blocking effects on the sympathetic intracortical circuits and/or sympathetic projections to and from the telencephalon. Cortical visual areas are involved, giving rise to imagery and light hallucinations. Auditory and gustatory effects are also noticed.

Most investigators have studied LSD-25 in nonpsychotic subjects to produce a "model psychosis." The similarity of the LSD-25 syndrome to that of schizophrenia has been affirmed by some workers; others have qualified their views or denied that there is more than a psychotoxic chemical effect. However, as Wikler (1957) has pointed out, "drugs which modify sensing, feeling, wishing, ideating—can be used as tools



ALBERT HOFMANN

*Perceptive Swiss chemist who discovered the hallucinogenic properties of* D*-lysergic acid diethylamide.*

"The psychotomimetics may be regarded as psychotropic drugs par excellance for they are distinguished from other classes in that in the appropriate dose they act specifically on the psyche without producing any serious disturbances of the autonomic nervous system of bodily functions, and in that their psychic effects are very profound and impressive."

to detect and manipulate the biochemical, physiological, and psychological variables that regulate these functions, and the more one can explain drug effects in such terms, the more readily can one construct concepts about the dynamic processes that underlie behavior, normal and abnormal."

When LSD-25 is administered to psychotic subjects in general, psychotic symptomatology is accentuated. Most studies have been concerned with schizophrenic patients. In these there may be an intensification of the symptoms; however, euphoria is mentioned as a common effect. Some workers have been unable to demonstrate significant changes in their patients ascribable to LSD-25.

There is a wide variability of response to LSD-25 among different individuals. It seems to affect different personalities in various ways and the response is influenced by the experimental situation. von Felsinger, Lasagna, and Beecher (1956) have stressed the relationship of the personality structure and the type of reaction induced by LSD-25. There is a correlation in the amount of induced change and the degree of pre-existing maladjustment of the person. One major difference between the LSD-25 induced state in a normal subject and the schizophrenic is the sense of detachment that the former exhibits. The LSD-25 treated normal subject, in most cases, retains contact with reality and recognizes the nature of the experimental situation despite the hallucinations and perceptual illusions; the schizophrenic patient has lost this degree of mental awareness.

Some psychiatrists have administered LSD-25 to schizophrenic patients, persons with psychopathic personality disorders, and obsessional neurotics, as an adjunct to psychotherapy. For example, they have expressed the view that past traumatic experiences which previously were kept secret, may be communicated under the influence of LSD-25. There have been numerous criticisms of the use of LSD-25 in this manner, indeed, other agents, *i.e.*, amobarbital sodium have been employed in a similar way in psychotherapy. One must conclude that the ultimate value of LSD-25 in the therapeutic process or diagnosis of mental illness remains to be established.

Tolerance to LSD-25 is rapidly developed. This occurs in 3 to 7 days of repeated administration. When tolerance is developed, a 4-fold dosage level is ineffective in producing the hallucinatory syndrome. This is unlike the protracted nature of mental illness, nevertheless, it does not rule out the incrimination of a metabolite of structure similar to LSD-25 to which the psychotic patient does not become tolerant. The psychotomimetic effects of LSD-25 have been ascribed to a blockade of serotonin in the central nervous system. Since both LSD-25 and its brom analog, D-2 brom lysergic acid diethylamide (BOL-148), are serotonin antagonists but only LSD-25 is psychotomimetic in man, it appears that its action is not through serotonin blockade (Isbell, *et al.* 1959).

A subject under the influence of LSD-25 loses his ability to concentrate on a specific, significant sensation *e.g.*, pain. His attention span is short for any single sensation and there is a kaleidoscopic change of feelings, of disaster, delightful images, a gregarious sense of well being which may be followed quickly by other sensory impressions. The psychic impact may last for as long as two weeks in some individuals.

These effects prompted the study of LSD-25 in terminal cancer patients as an analgesic agent. It is of interest that this substance compared favorably with meperidine or dihydromorphinone as the patients reported their pain sensations. The number of patients studied was small but significant. The LSD-25 analgesic effects were protracted and the patients, in some instances, commented upon their unconcern for their own deadly disease (Kast, 1964).

**Hazards of LSD-25 administration.** With the increasing use of LSD-25 in investigations in man, it is significant to point out that serious side effects and complications have been encountered. Cohen (1960) has reviewed these adverse reactions. In addition to the physical effects which are generally mild, periods of depression associated with attempts toward self-destruction and prolonged psychotic reactions have followed the LSD-25 experience. States of confusion, tenseness and panic episodes with terror have been described by some authors as associated with the administration of LSD-25. Cohen suggests that careful selection of subjects, constant attendance of a physician or trained person for sympathetic reassurance, a competent therapist who knows the nature of the reaction and who is prepared to handle a sudden upheaval of emotions, and the availability of measures to counteract the effect of LSD-25, are all essential to reduce the incidence of serious untoward effects.

The deleterious effects of LSD-25 administration have become clear in recent years. Latent psychotics have experienced a disintegration of their personality even after a single dose; long-continued LSD-25 experiences have subtly created a psychopathology (Grinker, 1963). The indiscriminate use of LSD-25 by college students and persons seeking to "expand their consciousness" is hazardous. People who are attracted to the hallucinogenic drugs are often those most likely to be harmed by them. The risks involved in the use of any of the numerous and readily available hallucinogens have been reviewed by Farnsworth (1963).

**Psychotomimetic agents.** A large number of chemical substances are known that produce hallucinations, disorientation, changes in thoughts, perception, and mood in man. While these agents produce effects that might be called experimental psychoses, like LSD-25 they do not truly mimic psychotic diseases in man (Carr, 1959). Bufotenine, N,N-dimethyl-5-hydroxytryptamine (dimethyl-serotonin); harmine, ([6 methyl-4,5-pyrido]-2,3)-9-methoxyindole; mescaline, 3,4,5-trimethoxyphenylethylamine; Sernyl, 1-(1-phenylcyclohexyl) piperidine; psilocybin, O-phosphoryl-4-hydroxy-N-dimethyltryptamine; and Ditran, N-ethyl-3-piperidylphenylcyclopentyl glycolate are examples of psychotomimetic agents. Not any of these substances is therapeutically useful (Jacobsen, 1963). Recently morning-glory seeds (*Rivea corymbosa*) have been found to contain amides of lysergic acid. Chewing the seeds produces hallucinations (Hofmann, 1961).

## Theories of Psychotropic Drug Actions

Avenues of approach to an understanding of drug actions in the brain have been the following:

*1. Neurotransmitter substances in the central nervous system.* The concept is proposed that enzyme inhibition by drugs will prevent chemical transmitter destruction.

*2. Biochemical-metabolic changes.* Enzymic and metabolic fragment interchanges at subcellular (mitochondrial) levels may be modified by drugs. Energy exchange in terms of glucose utilization and phosphate turnover is influenced. Blood flow changes in the brain may explain the effects of some drugs.

*3. Electrical functions of the brain.* Changes in electrical activity of specific brain regions are produced by drugs.

These basic concepts will be presented briefly. Reference is made to the mechanism of action of the individual drugs in discussing their pharmacology.

**Effects of neurotransmitters in the central nervous system.** A number of chemical substances have been identified in the brain which may function in the transmission of nerve impulses within the central nervous system. Most studies have been concerned with the catecholamines, epinephrine and norepinephrine, the indole, 5-hydroxytryptamine or serotonin, acetylcholine, and $\gamma$-aminobutyric acid. Definite evidence in support of the concept is lacking, but it is considered circumstantial that drugs that modify behavior, electrical activity in the brain, and biochemical processes elicit marked changes in the concentrations of these chemicals in specific areas of the central nervous system. It should be noted that the presence of particular chemical substances in a brain region does not necessarily presuppose a transmitter function. The evidence in favor of this concept is supported, however, in the case of cholinergic transmission in the central nervous system. One finds that regional distribution of acetylcholine in the brain is, in part at least, associated with the enzymes choline acetylase and cholinesterase.

*Role of serotonin.* The discovery of serotonin in the brain and the observations of Vogt (1954) that norepinephrine is also present and distributed in a manner similar to serotonin, has suggested that these agents act as chemical neuromediators. It has been proposed that reciprocal systems may function within the brain stem. Reserpine impairs the capacity of tissue cells to store serotonin; thus, the free amine is released to exert a pharmacologic effect. The major actions of reserpine, on the other hand, may be related to a loss of serotonin or norepinephrine by brain cells. The question remains whether the effects of reserpine are associated with the change in brain serotonin or with that of brain norepinephrine. Chlorpromazine, on the other hand, elicits a sedative response similar to reserpine, but apparently its action is not mediated through serotonin release. Chlorpromazine is assumed to inhibit the "sympathetic-like" system by blockade of the neurotransmitter, norepinephrine. Thus, chlorpromazine and reserpine act by different mechanisms to produce similar effects (Brodie and associates, 1959 *et seq.*).

By studying compounds that have a selective effect in releasing the amines serotonin and norepinephrine centrally, but not peripherally, and vice versa, and a compound that releases brain norepinephrine without releasing brain serotonin, it has been possible to shed light on the role of these amines in the action of reserpine (Brodie, 1960). The evidence indicates that the loss of brain norepinephrine is probably not the cause of reserpine-induced sedation. The enzyme monoamine oxidase (MAO) is thought to have an important role in regulating the norepinephrine and serotonin content of "storage" compartments of the brain cells. MAO inhibitors cause a rapid rise in the norepinephrine content of brain, sympathetic ganglia, and heart tissue (Spector, 1963). This action is believed to be associated with the behavioral stimulation produced in animals by the administration of MAO inhibitors.

Enzyme inhibition by drugs may exert a potent effect on the actions of neurotransmitter substances. A number of antidepressant drugs are inhibitors of monoamine oxidase. When animals are pretreated with MAO inhibitors, and then given reserpine, they are not sedated but are made hyperactive. The content of serotonin in the brain of these animals shows very little decrease. If the MAO inhibitors are given alone, an increase in serotonin in the brain, followed by an increase in norepinephrine, can be demonstrated. The concept that psychopharmacologic effects can be obtained by the administration of MAO inhibitor drugs has stimulated hundreds of studies in this field (Zeller, 1963).

The final answer to this remarkable quest to obtain efficient MAO blocking agents has not been obtained. Several entirely new kinds of enzyme inhibitors have been discovered with *in vitro* and *in vivo* activity. Certain of these agents have proved to be effective drugs and their actions are considered in this chapter. However, the subject has caused considerable controversy, and some workers contend that MAO has no important role in the inactivation of extraneuronal catecholamines (Kopin and Axelrod, 1963). The entire subject has been reviewed in a New York Academy of Sciences monograph (Zeller, 1963) and by Pletscher (1963).

Crossland (1960) has reviewed the evidence for chemical transmission in the central nervous system and has pointed out that recent studies have neglected the main body of investigations on acetylcholine and its related enzyme systems. It has been shown that acetylcholine has a stimulating action on the brain; further, under some circumstances it shows inhibitory effects. Drugs are known that produce sedation and excitation and at the same time modify the acetylcholine content of the brain. Acetylcholine obviously plays an important but poorly understood role in brain function. It is disappointing, as Crossland points out, that so far it has not been possible to find any general relationship between abnormalities of acetylcholine metabolism and the incidence of mental illness or nervous disease. While most workers are investigating other chemical transmitter substances, "there is no reason why they should be more likely than acetylcholine to hold the key to our final understanding of transmission in the brain."

The discovery of imidazole-N-methyl transferase, an enzyme that is responsible for the principal pathway of histamine metabolism, in the brain is likely of some significance in terms of the role of histamine in central nervous system function, page 922. It is remarkable that chlorpromazine inhibits the methylation of histamine by this enzyme. This action is antagonistic to the antihistaminic effects of chlorpromazine. The role of histamine in the brain in terms of behavioral effects is unknown.

**Biochemical-metabolic changes.** The significance of glucose utilization and oxygen consumption by the brain has been pointed out. Drugs can produce biochemical effects and behavioral changes. If cholinergic transmission or synaptic transmission by other neurotransmitters is accomplished by the synthesis of these substances, then psychoactive drugs might affect neural activity by lowering the supply of glucose and interfering with oxidative metabolism in the brain. Indirectly, the metabolism of noncarbohydrate substrates may be modified as are those of amino acids or fats. Chlorpromazine has been shown to inhibit cerebral oxidation and to inhibit ATP synthesis, but the drug concentrations far exceed therapeutic levels. Reserpine appears to have little influence on oxygen uptake, phosphorylation, or enzymic breakdown of high energy phosphate compounds.

Metabolic fragments of the psychotropic drugs may be the active form of these drugs in the central nervous system. In this case the individual metabolic pattern may determine the effectiveness of the drug in the particular patient. Indeed, this may be genetically determined, and pharmacogenetics is a new and significant aspect of drug actions in man and in animals. Brodie (1962) succinctly stated the issues relevant to biochemical and metabolic studies with psychotropic drugs:

> "Attempts to relate blood levels to therapeutic effects have been conspicuously missing in testing psychotherapeutic agents. For example, individual variation in response to chlorpromazine, as well as to other psychotherapeutic agents, has posed a provoking problem to the investigator. The fact that this drug might be inactivated at rates which vary by 500 per cent or more among different individuals is rarely considered. It might turn out to be more practical to attempt to relate variations in responses to concrete factors such as differences in drug metabolism before trying to relate them to abstract factors such as differences in personality structure. Moreover, the interpretations of carefully planned, double blind studies, especially those with fixed dosage schedules, might change considerably if it were known that the rate of inactivation had varied by several hundred per cent among individuals."

*Blood flow changes.* Since normal brain function is continuously and critically dependent upon the available supply of oxygen and glucose, it would be expected that biochemical and functional disorders would be associated with changes in brain circulation. Kety and his associates (1948 *et seq.*) and others have investigated cerebral blood flow changes *in vivo*, after the administration of drugs. Intravenously injected LSD-25 in doses that elicited the characteristic psychological effects, did not produce changes in cerebral blood flow, vascular resistance, oxygen or glucose utilization in either normal or schizophrenic subjects. A similar lack of change in cerebral blood flow has been found in schizophrenia during mental activity tests and after chlorpromazine. It is possible that drugs influencing behavior and abnormal mental conditions may be associated with changes in cerebral circulation and metabolism, but the area involved may represent a very small fraction of the total brain vascular supply. Since the over-all blood flow or metabolism is measured by this method, the effects could be obscured if they took place in a localized minute area.

Lewis *et al.* (1960) in an extension of this work with radioactive krypton ($Kr^{79}$), determined the cerebral blood flow and correcting for intracranial volume, found the rate to be 83 ml./100 ml. intracranial volume per minute. This figure is higher than the value obtained by the nitrous oxide method of 57 ml./100 gm. of brain tissue per minute. The $Kr^{79}$ method is sensitive to rapid changes in cerebral blood flow such as those induced by hyperventilation and norepinephrine infusion. By refinement of these technics it may be possible to measure the effect of drugs upon localized brain areas.

**Electrical functions in the brain.** Alterations in electrical activity within the central nervous system are produced by drug administration. The technics for this study require a conscious animal, and electrodes are implanted in such a way that the subject can move about freely. Animals immobilized with curare may be used, but obviously their behavior cannot be correlated with drug administration or electrical changes. In these experiments, special attention has been given to the reticular formation which receives and transmits corticipetal impulses. The term, ascending reticular formation, is used to designate this neuronal network that receives diffuse impulses and relays these to the cortex. It is proposed that these reticular impulses are essential to keep the cerebral cortex in a "waking state." Other areas in the brain also have a characteristic resting and waking electrical pattern that seems to be mediated through the ascending reticular system. Essentially, this is the basis for regarding this system, as related to states of consciousness, sleep, and wakefulness.

When no sensory impulses are received and transmitted by the reticular formation, a characteristic high voltage, slow wave pattern is recognized as synchronization in the EEG of the cortex. This is a sleeping or resting pattern. It can be recognized and associated with the resting or sleeping behavior of the animal. Surgical transection and isolation of the cortex from the ascending reticular formation produces a synchronization pattern.

The introduction of intense stimulating impulses into the reticular formation via sensory stimuli produces a desynchronization pattern in the cortex, with rapid, low voltage electrical impulses. In the thalamus, very regular high voltage waves of electrical activity are recorded. This is the awake, or alert, pattern. The "arousal reaction" is denoted by the change from the resting to the awake state.

Although there is some controversy, the majority of reports agree that chlorpromazine inhibits the EEG arousal pattern although not to the same degree as the barbiturates or scopolamine, atropine, or benactyzine. There seems to be a clear difference in effect between the hypnotics and chlorpromazine on the electrical function of the reticular system.

Reserpine produces an alert electroencephalographic pattern in contrast to barbiturates which evoke a pattern of sleep. Some workers have not found an alteration in EEG arousal patterns in animals, even when large doses of reserpine were used. Apparently, the effect obtained is related to the experimental situation, for some investigators have reported that reserpine will elicit periods of synchronization (resting pattern), alternating with periods of desynchronization (alert pattern).

Numerous other drugs, particularly the sympathomimetics and parasympathomimetics, have been studied for their effects upon the electrical activity of the ascending reticular formation. In general, behavioral arousal coincides with the desynchronization, arousal pattern, but a number of important exceptions must be explained. For example, the arousal evoked by sympathomimetic drugs is not associated with behavioral arousal; on the other hand, the resting pattern obtained after anticholinergic drugs is not followed by tranquilization.

Other studies of cerebral synaptic transmission have revealed that psychopharmacologic agents will inhibit transcallosal responses. Marrazzi and Hart (1955 *et seq.*) has shown that epinephrine, norepinephrine, mescaline, LSD-25, and serotonin have an inhibitory effect. Barbiturates also depress synaptic transmission, but chlorpromazine and reserpine have no effect. These two latter drugs will abolish the inhibitory effect of mescaline.

There is a rich literature dealing with EEG patterns in normal and psychotic states and the influence of drugs on the EEG. Recent attempts to make quantitative EEG analyses in schizophrenic subjects and to measure drug-induced changes have been fruitful. There is a difference between the spontaneous cortical electrical activity of normal subjects and chronic schizophrenic patients. In addition, there is a striking similarity between LSD-25-treated normal subjects and schizophrenic patients. A quantitative analysis illustrates these differences and similarities (Goldstein *et al.*, 1963). Future work of this character may serve to elucidate the finer details of brain functions and schizophrenic behavior and point the way to the study of basic drug effects in the central nervous system.

There are many problems presented in endeavoring to formulate a broad hypothesis involving the mechanism of action of the psychotropic drugs. Undoubtedly, an understanding of their pharmacologic actions will be richly rewarding in terms of understanding brain function and mental illness.

## The Psychotropic Drugs

Several classifications have been proposed for the drugs that are employed for their effects upon mental function in man. The general term "psychotropic" refers to any substance which alters mental processes or behavior. Psycholeptic agents have a depressing or inhibiting action. Thus, the sedative, tranquilizing, or ataractic drugs would be considered psycholeptics. Psychoanaleptics have a stimulating or enhancing action. The antidepressive drugs or psychostimulants are so classified. The psychodysleptics are drugs that exert a disorganizing or confusional effect. Psychotomimetic agents are examples of this class. There is no recognized therapeutic use of these agents at the present time. The term "tranquilizer" has restricted meaning and should not be used to designate the entire group of psychopharmacologic agents. In usual parlance, the term psychotropic refers to therapeutically useful psychopharmacologic drugs.

It is generally understood that a psycholeptic drug is one that elicits a calming effect, reducing anxiety, tension, agitated, or disturbed behavior. Unlike the barbiturates, these drugs should produce this relief of symptoms without causing a marked degree of sedation or sleepiness.

**Chemical classification of drugs used in mental illness.** Chemically, the psycholeptic drugs fall within four general classes. The first group of chemicals contain the phenothiazine nucleus and includes *chlorpromazine*, *promazine*, and others. The second group embraces the *Rauwolfia alkaloids reserpine*, *deserpidine*, *and rescinnamine*. The third group includes derivatives of *alkyl diols;* to this group belong *meprobamate*, *phenaglycodol* and others. The fourth classification comprises the derivatives of *diphenyl methane* and includes *benactyzine*, *hydroxyzine*, and others of miscellaneous structure. It is clear that these compounds have little in common as far as chemical constitution is concerned.

The antidepressive agents do not have a related chemical structure. *Imipramine* has a structural similarity to the phenothiazines; *isocarboxazid*, *nialamide*, and *phenelzine* are hydrazine derivatives; the other antidepressive drugs have miscellaneous structures.

**Pharmacologic classification of the psychotropic drugs.** It is apparent that since the biochemical lesions responsible for mental disturbance have not been delineated, the mechanism of the beneficial response to the psychotropic drugs cannot be described adequately. However, certain interesting observations have been made which shed some light upon their actions.

Berger (1963) classified the generally-used psycholeptic drugs into two categories. The first group affects the *autonomic* and *central nervous systems* and the second group affects only the *central nervous system* and has no autonomic component. The first group contains the phenothiazine derivatives, reserpine, and the diphenylmethane derivatives. The second group of central nervous system relaxants embraces meprobamate and phenaglycodol.

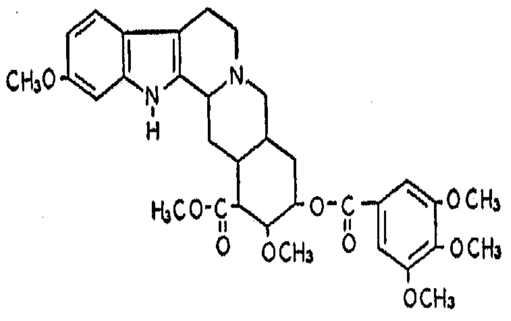
These two groups of drugs differ in many respects when consideration is given to their detailed pharmacologic action. The drugs in the first group, which may be called autonomic depressants, block conditioned responses and lower the threshold to electroshock and chemically-evoked seizures in animals. They potentiate the action of hypnotics and elicit characteristic changes in the electroencephalogram similar to those following large doses of atropine. In normal individuals they evoke a state of insulation from their environment and tend to produce mood depression. They likely act in a nonspecific manner on a variety of conditions by their actions on neuronal-regulating centers. Drugs in the second group of psycholeptics do not alter conditioned reflexes and have little effect on abnormal human behavior. They increase the threshold for electrical or chemical seizures. They do not affect the hypothalamic regulating centers or normal responsiveness to stimuli. However, they selectively reduce exaggerated responses.

**Discovery of new psychotropic drugs.** The initial discovery of the effectiveness of chlorpromazine and reserpine in treating the symptoms of severe psychotic patients was not based upon animal experimentation. After the psycholeptic effects of these drugs were observed in man, research strategy was built around animal behavior studies that might reflect the potential usefulness of candidate chemical compounds in mental diseases. Animal drug screening technics in psychopharmacology seek to discover new drugs and in addition may provide an understanding of the pharmacology of behavior. Unfortunately, not any of these tests are good predictors of the therapeutic use of psychopharmacologic agents in man. The most successful drug screening measures in animals are those that employ an experimental situation that is close to the human disease counterpart, *e.g.*, bacterial infections. This is impossible to do in psychopharmacology. We cannot replicate the psychoses and hallucinations of man in animals. For these reasons, most animal drug screening programs in psychopharmacology seek to find drugs that are equivalent to, or superior to, drugs known to be effective in various forms of mental illness. An appraisal of these technics has been made by Carr (1963).

**Therapeutic classes of psychotropic drugs.** Under the discussions of the individual drugs a more detailed account of their pharmacologic responses is given. Table 32-1 lists the psychotropic drugs according to clinical use. The major psycholeptic agents are those with apparent or confirmed efficacy in the treatment of psychotic patients. The minor psycholeptic agents are those used in the treatment of neurotic and psychosomatic reactions. The psychoanaleptics are used in the treatment of the depressions. These drugs will be discussed by groups considering the Rauwolfia alkaloids and chlorpromazine first because of their historic importance.

### THE PSYCHOLEPTIC DRUGS

**Reserpine, U.S.P.** Reserpine is an alkaloid obtained from the Indian plant *Rauwolfia serpentina*. The root of the plant was used by the natives of India in the treatment of the insane. The whole root, extracts of the root, and the alkaloid reserpine were introduced into occidental medicine in 1952 for the treatment of hypertension (page 681). In light of the discussion of the foregoing paragraphs it is important to note that reserpine contains an indole nucleus as is present in serotonin. Its structure is shown in the formula:



Reserpine, U.S.P.

**Neuropharmacologic effects of reserpine.** One of the sites of the action of the hypotensive effect of resperine is central. It was soon recognized that the drug evoked a tranquilizing action on the cerebrum which appeared to be produced by smaller doses than required for its hypotensive action. The two effects seemed to be independent of each other.

Sham rage in cats, characterized by general excitability, pupillary dilatation, contraction of the nictitating membrane, tachycardia, hypertension, and increased vascular reflexes, is produced by removal of the cerebral cortex. The release of the inhibitory functions of the cerebral cortex on the centers in the diencephalon pro-

TABLE 32-1

*Therapeutically Useful Psychotropic Drugs*

| Generic Name | Trade Name | Dosage mg. per day* | Manufacturer |
|---|---|---|---|
| | Major Psycholeptics | | |
| *Phenothiazine derivatives* | | | |
| acetophenazine dimaleate | Tindal | 40-80 | Schering Corporation |
| carphenazine maleate | Proketazine | 25-800 | Wyeth Laboratories |
| chlorpromazine HCl (U.S.P.) | Thorazine | 100-1600 | Smith, Kline & French Laboratories |
| fluphenazine di HCl | Prolixin | 2-20 | E. R. Squibb & Sons |
| mepazine HCl | Pacatal | 75-400 | Warner-Chilcott Laboratories |
| perphenazine | Trilafon | 6-48 | Schering Corporation |
| prochlorperazine maleate (U.S.P.) | Compazine | 15-50 | Smith, Kline & French Laboratories |
| ethanedisulfonate (U.S.P.) | | | |
| promazine HCl | Sparine | 75-1000 | Wyeth Laboratories |
| thiopropazate di HCl | Dartal | 30-100 | G. D. Searle & Co. |
| thioridazine HCl | Mellaril | 75-750 | Sandoz Pharmaceuticals |
| trifluoperazine di HCl | Stelazine | 3-24 | Smith, Kline & French Laboratories |
| triflupromazine HCl | Vesprin | 75-250 | E. R. Squibb & Sons |
| *Rauwolfia alkaloids* | | | |
| alseroxylon | many | 2-4 | many |
| deserpidine | Harmonyl | 1-6 | Abbott Laboratories |
| rescinnamine (N.F.) | Moderil | 0.5-1 | Chas. Pfizer & Co., Inc. |
| reserpine (U.S.P.) | many | 1-5 | many |
| | Minor Psycholeptics | | |
| *Phenothiazine derivatives* | | | |
| pipamazine† | Mornidine | 20-30 | G. D. Searle & Co. |
| promethazine HCl (U.S.P.) | Phenergan | 50-150 | Wyeth Laboratories |
| propiomazine HCl‡ | Largon | 10-30 | Wyeth Laboratories |
| triethylperazine maleate† | Torecan | 10-30 | Sandoz Pharmaceuticals |
| trimeprazine tartrate[a] | Temaril | 10-80 | Smith, Kline & French Laboratories |
| *Compounds of miscellaneous structure* | | | |
| azacyclonol HCl (N.F.) | Frenquel | 60-400 | The Wm. S. Merrell Co. |
| benactyzine HCl | Suavitil | 3-10 | Merck Sharp & Dohme Laboratories |
| buclizine HCl | Softran | 50-300 | Stuart Company |
| chlordiazepoxide, HCl | Librium | 10-100 | Hoffmann-La Roche, Inc. |
| diazepam | Valium | 4-40 | Hoffmann-LaRoche, Inc. |
| chlormethazanone | Trancopal | 200-400 | Winthrop Laboratories |
| chlorprothixine | Taractan | 50-500 | Hoffmann-LaRoche, Inc. |
| cyproheptadine HCl[b] | Periactin | 8-16 | Merck, Sharp & Dohme Laboratories |
| hydroxyphenamate | Listica | 600-800 | Armour Pharmaceutical Company |
| hydroxyzine HCl (N.F.) | Atarax | 30-75 | J. B. Roerig & Co. |
| pamoate | Vistaril | 75-100 | Chas. Pfizer & Co., Inc. |
| mephenoxalone | Trepidone | 1600-4800 | Lederle Laboratories |
| | Tranpoise | 1600-4800 | Whittier Laboratories |
| | Lenetran | 1600-4800 | Lakeside Laboratories |

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* Doses indicate comparative range and potency; not a guide for clinical use.

† Antiemetic with CNS activity, page 256.

‡ Preanesthetic adjunct with psycholeptic activity.

[a] Antipruritic with CNS activity, page 926.

[b] Anorexic with CNS activity.

TABLE 32-1—*Continued*

| Generic Name | Trade Name | Dosage mg. per day* | Manufacturer |
|---|---|---|---|
| prothipendyl HCl | Timovan | 100–400 | Ayerst Laboratories |
| *Substituted diols* | | | |
| meprobamate (U.S.P.) | Equanil, | 600–1600 | Wyeth Laboratories |
| | Miltown | 600–1600 | Wallace Laboratories |
| phenaglycodol | Ultran | 800–1800 | Eli Lilly & Company |
| emylcamate | Striatan | 600–1200 | Merck, Sharp & Dohme Laboratories |
| Major Psychoanaleptics | | | |
| amitriptyline HCl | Elavil | 50–300 | Merck, Sharp & Dohme Laboratories |
| imipramine HCl | Tofranil | 50–300 | Geigy Pharmaceuticals |
| methylphenidate HCl | Ritalin | 15–30 | Ciba Pharmaceutical Products, Inc. |
| pipradrol HCl (N.F.) | Meratran | 3–6 | Wm. S. Merrell Co. |
| *Monoamine oxidase inhibitors* | | | |
| isocarboxazid | Marplan | 10–30 | Hoffmann-LaRoche, Inc. |
| nialamide | Niamid | 25–200 | Chas. Pfizer & Co., Inc. |
| phenelzine-dihydrogen sulfate | Nardil | 15–45 | Warner Chilcott Laboratories |
| tranylcypromine sulfate | Parnate | 5–30 | Smith, Kline & French Laboratories |

duces the sham rage. The sham rage in cats is markedly, yet not completely, antagonized by reserpine. Full reserpine effect is seen only when the cerebral cortex is intact. Thus, it appears that reserpine intensifies the inhibitory functions of the cerebral cortex and facilitates synaptic neuronal transmission. Cholinergic predominance associated with the inhibition of afferent impulses results from the facilitation of cortical inhibitory activity.

Although reserpine has been shown to prolong the sleeping time of rats and mice induced by pentobarbital, the anticonvulsive action of phenobarbital and diphenylhydantoin to electrically-induced convulsion in mice is antagonized by reserpine. The antagonism between reserpine and these two central nervous system depressants appears to be competitive. Thus the action of reserpine on the cerebral cortex is quite different from the depression produced by the barbiturates. It involves an intensification of the inhibitory functions of the cortex. An alert encephalographic pattern is established, and different behavioral patterns become manifest.

The relationship of reserpine to cerebral serotonin metabolism is discussed in the previous section. Reserpine acts upon the hypothalamic centers, and this effect is associated with the endocrine disturbances this drug produces in animals and man. This subject has been reviewed by Khazan *et al.* (1962) for the entire group of psycholeptic drugs.

**Use of reserpine in psychotic states.** Nathan S. Kline pursued the original observations of R. H. Hakim of India who employed Rauwolfia and electroshock therapy in psychotic patients in 1953. Kline demonstrated a significant tranquilizing effect of Rauwolfia and reserpine in 400 mentally disturbed patients. The incidence of violent accidents, restraints, and seclusions was reduced. The drug therapy appeared to combat excessive inhibition and reticence, anxiety and obsessive compulsive drives. This was a remarkable discovery for at that time there was no known drug that would produce similar effects without concomitant sedation, ataxia, and soporific effects.

Various dosage schedules have been used, dependent upon the character of the patient's illness at the time therapy is instituted. The optimal dosage level is proportional to the intensity of the emotional disturbance. Chronic schizophrenic patients require an initial intramuscular dose of at least 5 to 10 mg. of reserpine plus 3 mg. orally. As improvement is experienced an oral daily dose of 2 to 8 mg. is used. There is no incompatibility between the reserpine regimen and electroshock therapy although some reports have stressed the respiratory difficulty which the patient may experience. Psychotherapy is also desirable concomitantly, and with reserpine the treatment may be facilitated. Reserpine therapy may cover a period of 3 to 4 months at the optimal dosage level.

Side reactions with reserpine are nasal stuffiness, tremulousness, and gastrointestinal distress. Drowsiness, bradycardia, hypotension, fatigue, and salivation are less frequently encountered. Occasionally, edema of the face and feet appear. From 2 to 5 per cent of the patients develop typical parkinsonism during the course of treatment. Reserpine is more effective in acute schizophrenics than in chronic patients.

**Alseroxylon** is a fat-soluble alkaloidal fraction extracted from the root of *Rauwolfia serpentina.* It is composed of reserpine and other nonadrenolytic amorphous alkaloids. Orally, 1 mg. of alseroxylon is approximately equivalent to 0.2 mg. of reserpine.

Reports of several controlled clinical trials with reserpine in psychoses (acute schizophrenia), anxious and tense patients, geriatric patients and childhood reading disorders have been less enthusiastic than were the earlier reports of uncontrolled studies (Cole *et al.* 1960). However, it has been pointed out that negative results are usually related to insufficient dosage and too short duration of medication.

With the availability of numerous other drugs that may be more effective and devoid of the potential toxicity of reserpine, the future of this drug in psychiatric practice is not secure. The mounting number of reports of severe depressions, gastrointestinal hemorrhage, peptic ulcer, increased epileptic seizures, and skin eruptions indicate caution in prescribing reserpine and the related alkaloids.

Although reserpine is used less frequently than previously, interest continues in the pharmacology of the Rauwolfia alkaloids. The 4 most important alkaloids used in therapy are reserpine, deserpidine, rescinnamine, and syrosingopine. The latter compound is used in the treatment of hypertension.

**Deserpidine (Harmonyl).** Deserpidine (11-desmethoxyreserpine) is an alkaloid obtained from *Rauwolfia canescens.* It is similar in chemical structure to reserpine, differing only by the absence of the methoxy group on the indole nucleus. Like reserpine, this alkaloid is used in the treatment of mild anxiety states or major mental illnesses. It is also employed in the treatment of mild hypertension.

The dosage schedule for deserpidine is 0.1 mg. orally daily in mild anxiety. For institutionalized, severely disturbed psychiatric patients not less than 2 to 3 mg. daily is likely to be effective. Deserpidine is available in 0.1 mg., 0.25 mg., and 1 mg. tablets.

**Rescinnamine N.F. (Moderil)** is 3,4,5-trimethoxycinnamyl methyl reserpate. This alkaloid is used in agitated patients with neuroses and severe psychoses. The incidence and severity of side effects, particularly sedation and bradycardia, are said to be less than the untoward reactions to reserpine.

Rescinnamine is administered orally usually in doses of 3 to 12 mg. for institutionalized psychotic patients. The usual therapeutic dosage schedules and precautions are observed as with reserpine.

Deserpidine and rescinnamine are claimed to have fewer side effects than reserpine. The few uncontrolled studies that have been reported do not offer significant evidence of any special usefulness.

### THE PHENOTHIAZINE PSYCHOLEPTICS (DIMETHYLAMINE SERIES)

Table 32-2 lists the drugs considered in this section. A description of the chemical and pharmacologic properties of each drug is given briefly. In the final section a general review of their clinical use is presented.

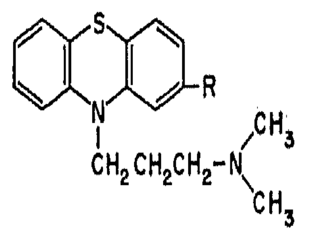
Table 32-2 gives the chemical structural relationships of the major phenothiazines. These will be considered as groups according to their chemical constitution. Chlorpromazine is a member of the dimethylamine series.

**Chlorpromazine Hydrochloride, U.S.P. (Thorazine).** For more than a decade French investigators have studied the derivatives of phenothiazine as antihistaminic drugs. It was observed that certain phenothiazines produced a feeling of lethargy, an "impression of annihilation" and anesthesia similar to that elicited by procaine. Winter in 1948 observed that the antihistaminic promethazine (Phenergan) caused a marked potentiation of barbiturate narcosis. While seeking a phenothiazine derivative with a more marked central action, Charpentier at the laboratories of Rhone-Poulenc-Specia synthesized the phenothiazine derivative chlorpromazine. The structure is shown in the following formula. One notes in the structure of the chlorpromazine

TABLE 32-2

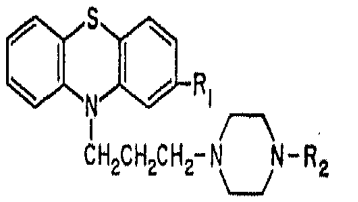
*The Phenothiazine Psycholeptic Agents*

Dimethylamine Series



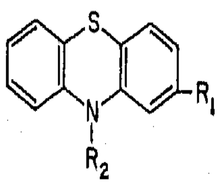
| R | |
|---|---|
| H | PROMAZINE (Sparine) |
| Cl | CHLORPROMAZINE (Thorazine) |
| $CF_3$ | TRIFLUPROMAZINE (Vesprin) |
| $OCH_3$ | METHOXYPROMAZINE (Tentone) |

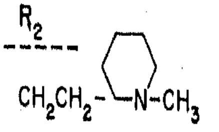
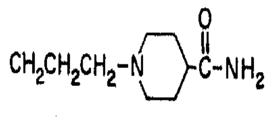
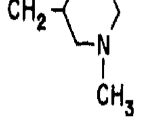
Piperazine Series



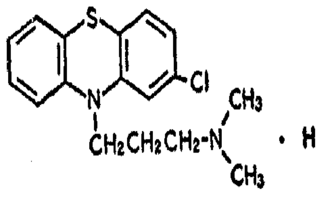
| $R_1$ | $R_2$ | |
|---|---|---|
| Cl | $CH_3$ | PROCHLORPERAZINE (Compazine) |
| $CF_3$ | $CH_3$ | TRIFLUOPERAZINE (Stelazine) |
| Cl | $(CH_2)_2OCOCH_3$ | THIOPROPAZATE (Dartal) |
| Cl | $(CH_2)_2OH$ | PERPHENAZINE (Trilafon) |
| $CF_3$ | $(CH_2)_2OH$ | FLUPHENAZINE (Prolixin, Permitil) |
| $COC_2H_5$ | $(CH_2)_2OH$ | CARPHENAZINE (PROKETAZINE) |
| $COCH_3$ | $(CH_2)_2OH$ | ACETOPHENAZINE (TINDAL) |

Piperidine Series



| $R_1$ | $R_2$ | |
|---|---|---|
| $SCH_3$ |  | THIORIDAZINE (Mellaril) |
| Cl |  | PIPAMAZINE (Mornidine) |
| H |  | MEPAZINE (Pacatal) |

molecule a striking similarity to the dye methylene blue.



Chlorpromazine Hydrochloride, U.S.P.
Thorazine
[10-(3-dimethylaminopropyl)-
2-chlorphenothiazine
hydrochloride]

Chlorpromazine hydrochloride is a white crystalline powder. It elicits a faint amine odor and is soluble in water, 1 gm./1 ml.

**Pharmacology of chlorpromazine.** Chlorpromazine evokes a multifaceted pharmacologic response in animals and man. The drug is rapidly absorbed orally, parenterally, or rectally. It produces local anesthesia of the mucous membranes which it contacts. The fate of the drug in the body is discussed on page 510.

Chlorpromazine administered to anesthetized dogs produces a tachycardia in doses of 1 to 5 mg./kg. With 10 mg./kg. there is a consistent fall in blood pressure. Cardiac output is reduced as a result of decreased peripheral resistance. The depressor effect and diminished cardiac output are likely due to adrenergic blocking which is one of the characteristic effects of chlorpromazine. At 10 mg./kg. the drug produces a flattening of the T-wave of the EKG. Larger doses evoke a marked cardiac acceleration with evidence of intraventricular block. During the hypotensive phase of chlorpromazine activity, there is no significant alteration of the glomerular filtration rate. Chlorpromazine in small parenteral doses evokes a mild degree of respiratory stimulation. Larger doses depress the rate and amplitude of respiration. During the period of depressed respiration, no apparent effect on the blood gas exchange has been noted.

Chlorpromazine is a relaxant to the smooth musculature of the intestine. It antagonizes the spasm produced in the rabbit's intestinal strip *in vitro* by pilocarpine. The motility of the gastrointestinal tract is inhibited by chlorpromazine as a result of its autonomic nervous system action. Large doses of chlorpromazine evoke a curare-like action on striated muscle. The oral $LD_{50}$ for mice for chlorpromazine is approximately 335 mg./kg. This figure provides an estimate of the relative toxicities of the related phenothiazines.

Electroencephalographic studies in animals and man show that chlorpromazine produces a pattern similar to that found in normal sleep. It does not evoke a rapid rhythm similar to the barbiturates. Further evidence of the central action of chlorpromazine is shown by its capacity to potentiate the action of anesthetics and sedatives. Chlorpromazine also has been shown to block the emesis elicited by apomorphine. The electroencephalographic findings are inadequate to explain the remarkable response to chlorpromazine in psychiatric therapy. The effects of chlorpromazine on electrical activity within the central nervous system, and its biochemical effects, have been described in the first portion of this chapter.

The multiplicity of the actions of chlorpromazine bespeak its use in many clinical conditions. Its effect in relieving nausea and vomiting is discussed on page 255. Its use in acute alcoholism is treated on page 289. The value of chlorpromazine in the relief of pain is discussed on page 312. It appears, however, that the principal use of the drug is in the management of psychiatric patients.

**Chlorpromazine in mental illness.** The use of chlorpromazine in mental illness stems from the work of Laborit (1952) who used chlorpromazine as one of the components of the "Lytic Cocktail" for the purpose of producing hypothermia and artificial hibernation for certain surgical procedures. The effect of chlorpromazine in tranquilizing states of agitation and anxiety attracted Delay *et al.* (1952), colleagues of Laborit to its use in psychiatric states.

In psychiatry chlorpromazine is indicated mainly for psychomotor states of agitation. It is effective in alleviating the various forms of tension, anxiety, and agitation, and in reducing the motor activity of psychoneurotics and psychotic patients.

Chlorpromazine has been found only moderately valuable in the treatment of depressive states. It does not appear to be able to combat serious cases of anxiety or melancholia. It is useful in some depressions, when anxiety and periods of stress and agitation are complications.

Chlorpromazine produces remarkable effects in schizophrenic patients exhibiting catatonia and paranoia. It elicits a serenity without a clouding of consciousness. The sedative and calming effects of the drug make it useful as an adjunct to other forms of therapy.

In senile and arteriosclerotic states chlorpromazine has been found useful in tranquilizing agitation, combativeness, confusion, and aimless wandering. The patient becomes more cooperative, and the problem of management is materially reduced.

After 10 years of use in medical practice, chlorpromazine has had a remarkable impact upon the practice of medicine. Ayd (1963) estimated that the drug has been prescribed for 50 million patients and that most physicians of the world have used it either as an antiemetic, a calming agent, in pain relief or to potentiate other drugs, and in ameliorating the symptoms of the severe psychoses. Although the drug has many side effects, these risks are relatively minor compared to the therapeutic benefit in most psychiatric patients. Therapy with chlorpromazine makes it possible to discharge from mental hospitals many chronically ill patients; others are improved so that they can be maintained on a quiet ward. Symptoms can be suppressed for a number of emotionally disturbed, anxious patients, and while not truly curative, the drug can be continued for years. The improvement in their behavior is sufficient to maintain them in the community.

In cancer patients chlorpromazine has been used successfully for 9 years to potentiate narcotics, to relieve emotional stress, and to control nausea and vomiting (Gibson, 1962).

In normal subjects, comparative studies with barbiturates and chlorpromazine in doses up to 200 mg. indicate that chlorpromazine impairs a variety of psychological functions including skill performance tests (Kornetsky and Humphries, 1958). The phenothiazine produces more residual psychological impairment the next day than a similar dose of secobarbital taken at night as a hypnotic. DiMascio *et al.* (1963) found that chlorpromazine, promethazine, perphenazine, and trifluoperazine produced psychomotor inhibition, mental confusion, autonomic alterations, and hypnosis in normal subjects. The latter two drugs produced psychomotor stimulation at certain dose levels. It was not possible to differentiate the psychiatrically effective agents from the ineffective promethazine. It was concluded that the clinical efficacy of these phenothiazine drugs in severely disturbed psychotic patients cannot be predicted from psychophysiologic actions in normal subjects; certainly their pharmacologic effects differ in these two groups.

**Dosage.** The dosage of chlorpromazine varies from patient to patient. For severely disturbed hospitalized psychotic patients, an initial deep intramuscular injection of 25 mg. is recommended. If this does not control the patient another 25 mg. may be given within an hour unless the drug is contraindicated by the presence of severe hypotension. Intramuscular doses may be increased up to 400 mg. every 4 to 6 hours. Oral doses may gradually replace parenteral therapy using 400 to 1000 mg. daily. When the patient improves, dosage levels are gradually reduced. Therapy must be continued for weeks or even months since frequently the effects are delayed. In patients who are less acutely agitated excellent results often are achieved with oral medication of 25 mg. 3 times a day initially. This may be increased to 100 to 400 mg. daily if improvement is not experienced. Undoubtedly, individual metabolic differences determine the dosage schedule for chlorpromazine and the other phenothiazine drugs.

**Toxic effects of chlorpromazine.** Many of the side effects and toxic reactions of chlorpromazine are typical of the group of phenothiazine drugs. The principal side effects that may be encountered with chlorpromazine therapy are *hypotension*, *hepatitis*, *dermatitis*, *potentiation of simultaneously administered sedatives*, *extrapyramidal symptoms*, and occasionally *agranulocytosis*. When a patient who is taking chlorpromazine develops gastrointestinal symptoms, fever, or anorexia, he should be observed closely for the appearance of jaundice. Neurotoxic symptoms of *akathisia*, or *parkinsonian-like tremors* may develop in certain patients on chlorpromazine therapy.

Although early studies showed no hepatic dysfunction produced by chlorpromazine, it is generally recognized that patients with existing hepatic disease show an increased responsiveness to the drug. This is related to the ineffectiveness of the impaired liver to metabolize the compound. Since the widespread use of chlorpromazine in this country, hepatitis has been a fairly frequent complication of therapy. Clinical recovery occurs when the drug is withdrawn. The hepatitis may be accompanied by an elevated thymol turbidity test and prothrombin deficiency indicative of parenchymal liver damage. The most common

type presents a clinical picture similar to obstructive jaundice with a moderate elevation of the alkaline phosphatase test. The other aspects of toxicity of the phenothiazines are discussed on page 509.

**Promazine hydrochloride (Sparine).** Chemically, the molecule of promazine is identical with that of chlorpromazine except that a hydrogen atom replaces the chlorine atom on the phenothiazine nucleus.

Promazine in most of its pharmacologic responses resembles the action of chlorpromazine. The presence of the chlorine atom in the molecule of chlorpromazine intensifies the central nervous system action of the compound. Therefore, the pharmacologic responses evoked by promazine in the main are less marked.

Promazine in doses of 1 to 3 mg./kg. injected intravenously into dogs evokes a mild characteristic depressor response of short duration. The effect is mediated mainly through adrenergic blockade since the drug blocks or reverses the pressor effect of epinephrine. At this dosage level there are no respiratory effects. Like chlorpromazine, promazine in large doses produces a curare-like action on skeletal muscle. Promazine produces a taming effect on monkeys; it will also retard motor activity and control mania and incoordinate muscular movements induced in the cat by the injection of morphine. Promazine prolongs the sleeping time produced by the barbiturates. The $LD_{50}$ of promazine administered orally to mice is 216 mg./kg. Toxic symptoms produced in animals include tremors, often running and leaping movements, followed by depression.

**Therapeutic indications of promazine.** Promazine is less potent than chlorpromazine in the treatment of acute neuropsychiatric agitation and the apprehension and anxiety of the acute psychoses. A number of reports conclude that promazine is less effective than chlorpromazine in the control of psychotic symptoms.

Promazine may produce agranulocytosis, leukopenia, and convulsions. Seizures and jaundice may pose serious clinical problems with promazine medication in some patients. Hypotension while frequently observed generally is not considered a serious problem. However, in elderly patients or subjects with a precariously balanced sympathetic nervous system, promazine may produce dangerous hypotensive effects.

Promazine hydrochloride is administered orally in doses ranging from 25 to 300 mg. daily. Dosage must be individualized. The smallest effective dose should be used. Intravenous dosage may produce severe hypotension.

**Triflupromazine (Vesprin).** Chemically, triflupromazine differs from chlorpromazine by replacement of the chlorine atom in the number 2 position on the ring, by a trifluoromethyl group. The resulting compound is more potent pharmacologically. Clinically, triflupromazine has a potency between chlorpromazine and prochlorperazine.

Triflupromazine is similar to the other phenothiazines in clinical use in chronic and acute psychoses. It is useful in the management of excessive psychomotor agitation and aggression in schizophrenia, and in mania and senile and toxic psychoses. The extrapyramidal side effects may be marked but these symptoms and the parkinsonian syndrome can be eliminated by reducing the dosage. The usual precautions of phenothiazine medication must be observed when triflupromazine is administered.

Triflupromazine hydrochloride is usually administered orally. It may be injected intramuscularly or intravenously in treating severely agitated patients or to control pernicious vomiting. The oral adult dose is 10 to 25 mg., twice daily. The dose should be individualized, and the amount gradually increased until the desired effects have been obtained. Severe side effects may limit the dose that can be administered. A dosage of 20 to 50 mg., 3 times a day, may be administered intramuscularly in severely agitated patients. The single intravenous dose is 2 to 10 mg. Oral dosage should be instituted as soon as possible.

### THE PHENOTHIAZINE PSYCHOLEPTICS
### (PIPERAZINE SERIES)

**Prochlorperazine, U.S.P. (Compazine).** Prochlorperazine is 2-chloro-10-[3-(1-methyl-4-piperazinyl)-propyl]-phenothiazine.

Prochlorperazine maleate occurs in a white or slightly yellow powder which is very sparingly soluble in water. Like chlorpromazine, prochlorperazine has a marked antiemetic activity. Based upon its protective power to prevent emesis in dogs after the administration of apomorphine, prochlorperazine appears to be about 5 times more potent than chlorpromazine. In rats prochlorperazine is 1.6 times more potent than chlorpromazine in blocking conditioned reflexes.

Prochlorperazine enhances the central depressant activity of barbiturates and morphine; however, it is much less active than chlorpromazine.

Prochlorperazine lowers blood pressure in anesthetized dogs when administered intravenously. Its hypotensive effect is about ½ that of chlorpromazine. Likewise the adrenergic blocking action of prochlorperazine is approximately ½ that of chlorpromazine. Prochlorperazine elicits antihistaminic activity and an antispasmodic action.

The acute toxicity of prochlorperazine upon oral administration to the mouse is low, $LD_{50}$ 2050 mg./kg.

**Clinical use of prochlorperazine.** Prochlorperazine is indicated in the treatment of nausea and vomiting and to relieve mild mental and emotional disturbances such as anxiety, tension, and agitation.

The principal value of prochlorperazine in the field of mental illness appears to be in severe psychiatric conditions, *e.g.*, schizophrenia, involutional psychoses, senile and toxic psychoses, mania, and degenerative mental states. In the Veterans Administration Third Cooperative Study, prochlorperazine was as effective as chlorpromazine in newly admitted, hospitalized schizophrenic patients (Casey 1960).

The dose of prochlorperazine is lower than chlorpromazine. On a weight basis the drug is approximately 5 times more potent than chlorpromazine. The general precautions of phenothiazine therapy must be observed.

Prochlorperazine maleate is given orally in tablets of 5, 10, and 25 mg. Parenterally it is available in solution as the ethanedisulfonate salt 5 mg./ml. and 10 mg./ml. Intramuscularly prochlorperazine is given in doses of 10 to 20 mg. to immediately control disturbed adults. The usual oral dose daily as an antiemetic and in mild anxiety states is 15 to 30 mg. daily. In severe psychosis the initial oral dose is 30 to 40 mg./day, in divided doses. The dose is increased gradually until the desired clinical response is obtained. The maximal dose may be as high as 80 to 100 mg. daily in hospitalized patients.

**Trifluoperazine (Stelazine).** Trifluoperazine is 10-[3-(1-methyl-4-piperazinyl)-propyl]-2-trifluoromethylphenothiazine. This is a potent phenothiazine and the clinically effective dose is much smaller than chlorpromazine. However, the drug does produce parkinsonian-like tremors, restlessness, tremulousness, and agitation even in the low doses. The extrapyramidal side effects can be controlled by reducing the dosage or administering antiparkinsonian drugs.

Pharmacologically, trifluoperazine resembles the related phenothiazines but it is more potent. Thus, trifluoperazine blocks the conditioned response of rats in the conditioned avoidance response situation, in approximately 1/10 the dose of chlorpromazine. It reduces spontaneous motor activity of rats and mice, elicits an antiemetic effect and potentiates barbiturate hypnosis in a manner similar to chlorpromazine but with smaller doses.

In chronic schizophrenics, oral doses of 2 to 5 mg., 2 to 4 times daily have been used. This dosage may be gradually increased until therapeutic benefits are achieved or side effects appear. Doses of 1 to 2 mg. twice a day have been used in treating hyperactive, emotionally disturbed children. Because of the high incidence of extrapyramidal disorders at the higher dosages, patients receiving trifluoperazine should be hospitalized or under very close supervision, if the daily oral dose exceeds 8 mg.

**Thiopropazate (Dartal).** Thiopropazate is used in the control of excessive psychomotor activity in minor and major agitation states. Chemically it is 1-(2-acetoxyethyl)-4-[3-(2-chloro-10-phenothiazinyl) propyl] piperazine dihydrochloride. The salt is a white crystalline powder readily soluble in water.

Thiopropazate elicits antiemetic and sedating effects in dogs. It produces a moderate, transient increase in heart rate and some hypotensive effect on the blood pressure of this species. Thiopropazate prolongs the barbiturate sleeping time of dogs. In clinically effective doses, thiopropazate does not ordinarily produce a significant change in the electroencephalogram. In this respect this drug differs from chlorpromazine which produces a synchronization of spontaneous cortical electrical activity in most cases.

Thiopropazate is used in the treatment of emotional disorders associated with mild neuroses or the severe psychoses. It is effective in controlling agitation, anxiety, and aggressiveness in chronic schizophrenic patients without producing undue sedation. The drug is more potent than chlorpromazine, and in general most reports indicate a lower incidence of central depression and autonomic blockade. Extrapyramidal symptoms have been encountered very frequently.

For anxiety and tension states in the neuroses, an initial 5 mg. oral dose is administered 3 times daily. This dosage is increased or decreased at intervals of 3 to 4 days according to the response of the patient. In psychotic conditions the initial dose is 10 mg., 3 times daily adjusted after 3 or 4 days as the therapeutic response indicates. The usual side effects of the other phenothiazine drugs may be expected. The parasympathetic effects of blurred vision, hypotension, constipation, and xerostomia are ordinarily mild. Skin reactions have seldom been reported.

**Perphenazine (Trilafon).** Perphenazine is 1-(2-hydroxyethyl)-4-[3(2-chloro-10-phenothiazyl)-propyl]-piperazine. Its activity as a tranquilizer is approximately 6 times greater than that of chlorpromazine.

Perphenazine is a white crystalline powder which is insoluble in water but soluble in organic and inorganic acids to form the corresponding salts. The hydrochloride is water soluble and comparable in its activity to the free base.

The action of perphenazine on the mouse, rat, cat, dog, and monkey is qualitatively similar to that of chlorpromazine. Quantitatively it is about 6 times more potent and approximately ½ as toxic. Perphenazine elicits a greater degree of behavior depression accompanied by muscle weakness and ataxia than does chlorpromazine.

**Clinical uses of perphenazine.** Perphenazine is useful in the treatment of mild anxiety states and in major types of psychotic disorders. It also elicits powerful antiemetic action, extending its clinical use to the treatment of nausea and vomiting of pregnancy, the nausea of tension headaches, and gastrointestinal distress.

Perphenazine has been established as a potent psycholeptic agent effective in the treatment of psychoneuroses associated with anxiety, tension, and agitation. Its effects are grossly similar to those of chlorpromazine. It causes a high incidence of extrapyramidal symptoms with dystonias and dyskinesias characterized by spasmodic contractions of the muscles of the tongue, mouth, neck, and shoulder girdle. The usual precautions of phenothiazine therapy must be observed with perphenazine.

Perphenazine is available in tablets containing 2, 4, 8, and 16 mg. Patients are started on 2 or 4 mg. 3 times a day. These doses are usually adequate to treat psychoneuroses. In severe psychoses the total oral adult dose ranges from 16 to 64 mg. per day administered in divided doses. Intramuscular injections of 5 mg. repeated every 6 hours, may be necessary for the prompt control of acute episodes. Perphenazine is available for parenteral administration in solution 5 mg./ml.

**Fluphenazine (Prolixin, Permitil).** Fluphenazine is a very potent phenothiazine. The drug is 4-{3-[2-(trifluoromethyl)-10-phenothiazinyl]propyl}-1-piperazine ethanol dihydrochloride. It has antiemetic, antianxiety, and mild sedative actions.

Fluphenazine has been used in the treatment of a variety of mental disorders and behavioral disturbances characterized by anxiety, tension, and emotional instability. It has been used with some success in schizophrenia, mania, senile psychoses, and mental disorders associated with organic brain disease, especially where agitation, excitement, aggression, hallucinations, and delusions are prominent. In general, the drug is very effective in some patients, has a rapid onset of action but produces a high incidence of extrapyramidal side effects. Unless low dosage is also associated with a lower incidence of extrapyramidal symptoms and autonomic side effects, it offers no therapeutic advantage. What is desired is a phenothiazine derivative that is sufficiently potent but without neurologic side effects.

The adult oral dose of fluphenazine is 2.5 to 10 mg. daily adjusted to the patient's needs. Several clinical trials have indicated that a single daily dose of 1 to 5 mg. may be sufficient for maintenance therapy. *Permitil* is a low dosage form, 0.25 mg. tablet of this drug.

**Carphenazine maleate (Proketazine).** Carphenazine is a short-acting antipsychotic drug introduced for the management of schizophrenic patients under hospitalized conditions. It is used in treating the symptoms of acute or chronic schizophrenia. Its clinical uses and activity resemble the other members of the piperazine group of phenothiazine drugs. It has the same contraindications. The drug will produce somnolence and extrapyramidal symptoms in certain patients, especially when large doses are administered.

Carphenazine maleate dosage is individualized for each patient. Initially the dose should be low and gradually increased to optimal levels by weekly or biweekly increments. The usual dosage range is from 25 to 400 mg. per day. In chronic schizophrenic patients who have experienced symptoms of regression, withdrawal, mutism, apathy, bizarre posturing, seclusiveness, delusions, or hallucinations for more than 3 years a dose of 25 to 50 mg. 3 times daily may be used initially. Unfortunately, very few controlled studies have been reported on carphenazine so that its relative effectiveness cannot be evaluated at this time.

**Acetophenazine maleate (Tindal).** Acetophenazine is a piperazine phenothiazine derivative used as a calming agent with a mild sedative effect. It has the same chemical structure as carphenazine except for the $-COCH_3$ substitution in the number 2 position on the phenothiazine ring.

Acetophenazine apparently lacks an effect upon the brain stem in the relatively low doses used in treating anxiety and tension states. In these doses extrapyramidal reactions have not been reported. At the larger doses required for psychotic patients, extrapyramidal symptoms and other effects commonly associated with the administration of the potent phenothiazines are elicited.

The usual dosage of acetophenazine is 20 mg. 3 times daily although the dosage must be individualized. Doses range from 40 to 80 mg. per day. At these dosage levels acetophenazine may frequently produce drowsiness, weakness, and the parasympathetic effects associated with the administration of the phenothiazine drugs. For the present, use of the drug is limited to calming agitated and mildly disturbed nonpsychotic patients.

### THE PHENOTHIAZINE PSYCHOLEPTICS (PIPERIDINE SERIES)

**Thioridazine (Mellaril).** Thioridazine is unique in that a thiomethyl group replaces the chlorine atom in position 2 on the phenothiazine ring. The compound is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl)-ethyl] phenothiazine hydrochloride.

The pharmacologic actions of thioridazine are in general similar to those of the other phenothiazines with certain major exceptions. It does not produce the cataleptic-like state in various animal species that chlorpromazine elicits. A relationship is thought to exist between drug-induced catalepsy in the rat and drug-induced extrapyramidal symptoms in man. This observation may be associated with the low incidence of striopallidal complications of thioridazine therapy in man.

The antiemetic activity of thioridazine against apomorphine emesis in dogs is very low. In man this drug is not an antiemetic in usual therapeutic doses. This pharmacologic difference of this phenothiazine has been related to its low incidence of extrapyramidal side effects. Thioridazine is approximately $\frac{1}{10}$ as potent in blocking the conditioned escape response in rats as chlorpromazine. It is approximately $\frac{1}{4}$ as potent as chlorpromazine in reducing spontaneous motor activity in the mouse. Its hypothermic effect in the rat is also weaker.

Thioridazine exhibits marked sympatholytic action *in vitro* on isolated organ preparations; however, *in vivo* the adrenergic blocking effect is very weak. In man, dryness of the mouth and minor autonomic nervous system effects have been reported.

**Clinical use of thioridazine.** Thioridazine appears to be as potent as chlorpromazine in a variety of psychosomatic and psychiatric conditions. It is apparently much less likely to cause extrapyramidal side effects. In some studies thioridazine proved to be somewhat more effective than chlorpromazine in psychotics and severe neurotics. This drug resembles chlorpromazine in its wide dosage range, the production of drowsiness, and the milder forms of autonomic side effects (Azima *et al.* 1959).

Some workers have speculated that only those phenothiazine drugs that are capable of producing extrapyramidal effects are useful in treating severe states of schizophrenia and in treating chronic psychotics with agitation and violent, hyperkinetic episodes. The effectiveness of thioridazine in these patients without producing marked extrapyramidal symptoms is of theoretical as well as practical importance.

Jaundice has not been reported following thioridazine therapy, and only a few cases of skin sensitivity have been observed. In general, the side effects resemble the other phenothiazine drugs. Administration of large doses of thioridazine has been found to produce pigmentary retinopathy. This is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision. Deposits of pigment may appear on the fundus, and edema may be produced several weeks later. This syndrome has not been observed in patients receiving less than 1.6 gm. per day. Reversible impairment of vision, without detectable retinal changes, was reported in a patient receiving a daily dosage of 400 mg. However, 1 month earlier this subject received 1.2 gm. per day for 12 days.

Thioridazine is administered orally to adults in doses of 10 mg., 3 times daily, in states of mild anxiety, apprehension, and tension. In the control of more severe agitation in psychoneuroses, alcoholism, and emotional disturbances doses of 25 mg., 3 times a day, are used. In agitated, hospitalized psychotics doses of from 200 to 800 mg. per day have been used. Dosage must be individualized and the smallest effective dosage determined for each patient. The same precautions that are followed when other phenothiazine drugs are administered must be observed.

**Mepazine (Pacatal).** Mepazine is 10-[(1-methyl-3-piperidyl)methyl] phenothiazine. The acetate is a white, crystalline powder suitable for parenteral use. The hydrochloride is the usual oral dosage form.

The principal pharmacologic responses to mepazine are similar to those elicited by chlorpromazine. Orally, in the rat, the $LD_{50}$ of mepazine is about 1000 mg./kg. Administered to animals, mepazine produces mild sedation without hypnosis; large doses produce sleep. Mepazine potentiates the effect of hypnotics, analgesics, and the local anesthetic action of procaine.

Mepazine augments the carotid sinus reflex in cats whereas chlorpromazine produces an inhibition. The drug has some antifibrillatory action, and it reduces a coronary spasm induced experimentally. The hypotensive action of mepazine is weak although the drug produces both pressor and vasodilator effects. Mepazine produces hypothermia, but its action is not marked. These actions of mepazine indicate that this drug elicits a variety of pharmacologic effects that differ from the other phenothiazine derivatives.

**Clinical use of mepazine.** Mepazine is less potent and less effective than chlorpromazine in the control of severe states of agitation, and the drug is not very useful in acute or chronic psychotic disturbances. Mepazine is most useful in calming states of anxiety, tension, and agitation in neuroses and increased psychomotor activity. It has been used with limited success in anxiety states, schizophrenia, alcoholic psychoses, and in the narcotic withdrawal syndrome.

In the Third Veterans Administration Cooperative Study, mepazine was relatively weaker than the 4 related phenothiazines (Casey 1960).

In the various clinical studies with mepazine several troublesome and some dangerous side effects have been encountered. These include xerostomia, visual disturbances, dizziness, nausea, vomiting, and postural hypotension in a few cases. Bladder atonia, marked constipation, and paralytic ileus have resulted from mepazine therapy. Jaundice, toxic psychoses, and granulocytopenia have also resulted from mepazine administration.

The dosage of mepazine hydrochloride varies from 75 to 600 mg. daily in divided doses orally. Maintenance dosage for severe psychiatric, hospitalized patients is usually 400 mg. per day, or more. Doses of 50 to 100 mg. per day are adequate for the treatment of nausea and vomiting. In severe states of agitation, 50 mg. of mepazine acetate may be injected intramuscularly or intravenously.

### THERAPY WITH PHENOTHIAZINE DRUGS

**Toxicity of the phenothiazine drugs.** The principal side effects and toxic reactions produced by the various phenothiazine derivatives have been mentioned in discussing the individual drugs. The drug-induced extrapyramidal symptoms vary in frequency, type, and severity depending upon the particular drug. In a comparative study of 3 antiparkinson agents in treating the symptoms of poverty of movement, facial fixity, and various degrees of akathisia, Kruse (1960) found benztropine (Cogentin), procyclidine (Kemadrin), and ethopropazine (Parsidol) to have about the same degree of effectiveness. Benztropine methanesulfonate or procyclidine hydrochloride were preferred where sialorrhea was prominent, and ethopropazine hydrochloride was superior in treating the dry mouth and visual blurring. Most difficult to treat was the akathisia; best results were obtained with procyclidine. This study in general supports the views of most workers concerned with treating the extrapyramidal symptoms of phenothiazine therapy.

Barbiturates administered cautiously in suitable dosage will control these neuromuscular side effects. Intramuscular injections of diphenhydramine hydrochloride (Benadryl) solution in doses of 20 to 50 mg. every 2 to 3 hours, as required, have been found to be especially effective in relieving these symptoms. The mechanism of action of diphenhydramine in treating these extrapyramidal reactions is unknown.

Agranulocytosis is the most serious complication produced by the phenothiazine drugs. Periodic hematologic examinations are wise precautions during therapy.

In treating the hypotension produced by phenothiazine medication, it is important to keep in mind that the pressor effect of epinephrine is reversed by these drugs. For this reason epinephrine should not be used. Phenylephrine, mephentermine, or a similar sympathomimetic amine should be employed.

**Metabolism of the phenothiazine drugs.** Despite the wide use of these drugs, very little information is available on their metabolic fate and excretion characteristics. Studies in psychiatric patients have clearly indicated marked therapeutic differences in individual patients and striking metabolic differences. It has been extremely difficult to correlate these two differences because (1) it is hard to assess quantitatively clinical change under drug therapy, and (2) chemical analytic methods for the phenothiazine drugs and their metabolites are not sufficiently precise when employed in excretion tests. Because the efficacy of the phenothiazine derivatives has been proved in schizophrenia, it is difficult to explain individual variations in drug response and rate of relapse following cessation of dosage, unless these differences are based upon individual absorption or metabolic variables. Reliable and sensitive chemical methods for these drugs and their metabolites would likely permit these questions to be answered.

There seems to be general agreement that the following derivatives of the phenothiazine drugs are excreted in the urine of human subjects under phenothiazine medication: chlorpromazine sulfoxide, the mono and didemethylated forms of chlorpromazine; their glucuronide(s) and sulfoxides. Similar sulfoxide metabolites, which may include N-demethylated sulfoxides, have been found for promazine and methoxypromazine. The hydroxylated derivatives in the 3 and 7 positions have been found in the urine in the free form and as glucuronides. These metabolic fragments may shed light on the mechanism of action of these drugs and may explain the many facets of their pharmacologic effects.

There is at present no information that correlates the dose of the phenothiazine drugs with blood, tissue or urine levels. Methods have been developed to detect the various phenothiazine compounds in the urine (Forrest and Forrest 1963). These tests are semi-quantitative and are useful to insure that the drug has been taken and confirm the diagnosis of phenothiazine-induced extrapyramidal effects to avoid mistaking these for an aggravation of the patient's psychopathology. Many patients excrete degradation products of the phenothiazines for 3 to 10 weeks after discontinuing therapy. There may be an association between excretion rate and remission of symptoms in these patients. As more psychiatric patients are maintained in their homes under medication, these subjects will be seen by the physician only at intervals. An accurate chemical urine test would be extremely useful to determine whether or not the patient had been taking the phenothiazine medication. It is known that about 50 per cent of the dose of chlorpromazine is excreted in the urine as unchanged drug and metabolites when the patient is receiving daily medication.

**Choice of phenothiazines in psychiatric and psychosomatic conditions.** It is very difficult to appraise the value of so many closely related drugs when controlled clinical trials have not been conducted. Cole, *et al.* (1960) reviewed the enormous literature on this subject and reported in their survey the results of the better controlled studies.

Chlorpromazine is the most widely used phenothiazine, and its superiority in schizophrenia and other psychoses, over other treatments, stands out consistently. While perphenazine (Trilafon), prochlorperazine (Compazine), trifluoperazine (Stelazine) and triflupromazine (Vesprin) are grossly similar and about as effective as chlorpromazine in lower dosage, they appear more likely to cause extrapyramidal side effects.

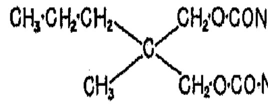
Special interest attaches to thioridazine (Mellaril) because it is as potent as chlorpromazine and produces fewer undesirable extrapyramidal symptoms. It is as effective as chlorpromazine in severe neurotic patients and in the treatment of psychoses. Its action appears to be more selective on the brain regions concerned with psychic relaxation without autonomic nervous system effects.

The lack of antiemetic effect of thioridazine is of interest when compared with other phenothiazine derivatives. Several phenothiazines are very effective antiemetic drugs but have weak antipsychotic properties; pipamazine (Mornidine) is an example. It remains to be established whether there is any relationship between these two properties. Certainly, smaller doses of more potent phenothiazines do not lead to fewer extrapyramidal effects produced by these drugs.

Winkelman (1960) reported excellent therapeutic results in 75 selected acute psychotic patients who were maintained on chlorpromazine therapy for 6 years. Optimal therapeutic results, however, were achieved only with intensive psychotherapy. In view of the accumulated experience with chlorpromazine it appears to be the drug of choice at the present time (Ayd, 1963).

### Miscellaneous Psycholeptic Drugs

**Meprobamate, U.S.P. (Miltown, Equanil).** Meprobamate is chemically related to mephenesin. The action of mephenesin is short because of the rapid oxidation of the primary hydroxyl group in the molecule. In an effort to block the oxidation and thus prolong the action, the hydroxyl group was converted to a carbamate. Meprobamate, the resulting compound, proved to have novel central nervous system effects not associated with the action of mephenesin. Chemically, meprobamate is 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate as shown by the following formula:



Meprobamate, U.S.P.

Meprobamate is a white crystalline powder eliciting a characteristic bitter taste. It is sparingly soluble in water.

**Pharmacologic action of meprobamate.** The pharmacologic studies of Berger (1954) showed that meprobamate produced a reversible flaccid paralysis of skeletal muscle. Autonomic functions and respiration were not significantly affected at these dosage levels. Smaller doses elicited only muscular relaxation and sedation. Meprobamate was observed to antagonize the convulsive seizures evoked by either strychnine or pentylenetetrazol. Anesthesia with the barbiturates was prolonged by meprobamate. The administration of the drug produced a taming effect upon monkeys. Viciousness was diminished. The drug also counteracted the irritability, aggressiveness, and the exaggerated startle response of rats with septal brain lesions. Meprobamate did not interfere with conditioned responses in the rat and several other species.

Meprobamate exhibits a depressant effect on multineuronal reflexes which lasts 8 times as long as mephenesin. It does not significantly affect monosynaptic reflexes.

Low doses of meprobamate decrease the frequency and increase the voltage of the electrical activity of the brain of the cat. The changes are more apparent in readings from the diencephalon than from the cerebral cortex. Baird *et al.* (1957) demonstrated that the effect of meprobamate on the electrical activity of the brain was not limited to the diencephalon, but extends to the forebrain ganglia (amygdala, caudate nucleus, pallidum) in varying degrees. These ganglia were found to exhibit different degrees of susceptibility to meprobamate. Lesions in the caudate nucleus may induce a supersensitivity of the pallidum to the action of meprobamate.

A characteristic action of meprobamate is its specificity for the thalamus. It does not depress cerebral cortical activity, and the characteristic spindling of the EEG produced by barbiturates does not usually occur after normal doses. Sustained high dosage of meprobamate produces EEG patterns that are similar to those elicited by barbiturates. There are, however, significant differences in the EEG observed after the two drugs (Berger, 1963).

In summary, the action of meprobamate in psychoneuroses and anxiety states may be due to its capacity to block selectively interneuronal circuits (thalamocortical and corticothalamic) and to the reduction of exaggerated reflexes to the usual magnitude (Berger, 1963). The relaxation of skeletal muscle is an additional component of the action of meprobamate; this it shares with mephenesin.

Berger (1954) suggests that the long latent period of action of meprobamate is likely due to its biotransformation in the tissues prior to its effective action. About 10 per cent of the drug is excreted in the urine unchanged within 24 hours. Patients receiving meprobamate by chronic administration excrete more of the degradation products, and the enzymic detoxification process is stimulated in a manner characteristic for many drugs.

Colorimetric methods are available for the detection of the drug in plasma, serum, spinal fluid, and urine (Hoffman and Ludwig, 1959).

Meprobamate is uniformly distributed in the brain of animals, and the drug does not tend to concentrate in a specific region (Emmerson, *et al.* 1960 *et seq.*). Urinary excretion products are unchanged meprobamate, 2-methyl-2-(β-hydroxypropyl)-1,3-propanediol dicarbamate, and a N-glucosyluronide conjugate of meprobamate. The hydroxy derivative is very water soluble, relatively nontoxic and is pharmacologically very weak. This example may be cited as a true detoxification product of the parent drug.

**Clinical use of meprobamate.** There is perhaps no other drug introduced in recent years which has had such wide use as has meprobamate. As a tranquilizer, without an automatic component in its action, and with few side effects, meprobamate has been used in anxiety states and many organic diseases with a tension component. It is impossible within the scope of this text to evaluate the volumes that have appeared on the use of meprobamate, therefore only certain cogent clinical summaries are included.

Meprobamate, like the related minor tranquilizers considered in this chapter, produces a mild degree of central nervous system depressant effects in the usual therapeutic doses. The ability to produce a psychosedative, skeletal muscle relaxant action with a soporific effect in most patients, accounts for the popularity of the drug. The distinction of these actions from the typical effects of the barbiturates is difficult. According to Berger (1963) there are significant differences.

The principal use of meprobamate is in anxiety of recent origin in patients suffering from an acute situational reaction. Extending this application to the overlay of anxiety attendant upon many organic diseases increases the therapeutic spectrum of meprobamate to many phases of medical practice. For example, meprobamate has been used in expediting and abetting the course of postoperative care and in quieting psychomotor agitation and anxiety in the treatment of alcoholism. Meprobamate has been used in the treatment of a wide variety of children of all ages manifesting prominent symptoms of anxiety and tension with or without organic disease. The drug was also found useful in the control of idiopathic *petit mal* epilepsy.

Meprobamate has been reported as beneficial in musculoskeletal disorders, orthopedic conditions, muscle spasm of fibrositis, and other rheumatic conditions. In these states the action is as a skeletal muscle relaxant and psychosedative to relieve anxiety.

A number of studies have reported meprobamate a useful drug as an adjunct in the treatment of hypertension and associated cardiovascular disorders. In these conditions the drug may be of benefit in providing symptomatic relief of the emotional concomitants of these diseases. This action has been described as easing the patient's adjustment to his condition. The drug has been administered with the organic nitrates for the symptomatic treatment of coronary artery insufficiency.

Meprobamate has been extensively employed in gastrointestinal distress such as nausea, eructation, diarrhea, and anorexia. As the sedative component in ulcer therapy, meprobamate is preferred by some clinicians to phenobarbital. The widespread use of this therapy is evinced by the combination of the anticholinergic agent Pathilon 25 mg. with 400 mg. of meprobamate known as *Pathibamate* for the treatment of peptic ulcer and allied conditions. Another such combination is *Milpath.*

In a critical and comprehensive review of studies of the efficacy of meprobamate in the treatment of anxiety, Laties and Weiss (1958) observed that the available evidence from controlled investigations does not provide firm conclusions indicating that meprobamate is superior to either a barbiturate or a placebo. There is need for more carefully controlled and better designed studies of the effectiveness of meprobamate in neurotic outpatients. It is possible that the action of meprobamate is different from that of the barbiturates, and that certain patients will respond to one drug better than the other. This difference has not been proved.

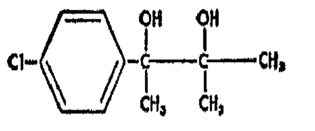
**Side effects of meprobamate.** The side effects of meprobamate are usually of a minor nature; however, the drug may produce severe reactions and indiscriminate use is to be condemned. Meprobamate produces hypersensitivity reactions including urticaria and erythematous and maculopapular skin rashes with pruritus. Chills and fever may occur. Nonthrombocytopenic purpura and ecchymoses with fever and peripheral edema have resulted from meprobamate administration. Considering the widespread use of this drug the incidence of untoward effects is low. Other effects include drowsiness, headaches, vertigo, syncope, fever, seizures, diplopia, and paradoxical excitement. Severe and fatal hypersensitivity reactions have been reported. The treatment of these cases is symptomatic, and the drug should be discontinued.

Patients who are known to have a propensity for taking excessive quantities of drugs, *e.g.*, barbiturates or alcohol, should be carefully supervised if meprobamate is prescribed for them. A feeling of being less tense and the exaggerated sense of well being, even to the point of euphoria, has led to excessive overdosage. Under the influence of the drug a form of incoordination may be produced, by large doses especially, that resembles alcoholic intoxication.

Ewing and Haizlip (1958), in a controlled study, confirmed the observations that meprobamate in large doses of 3.2 to 6.4 gm. a day would produce physical dependence in psychiatric patients. Their patients developed barbiturate-like withdrawal symptoms when the drug was abruptly stopped. When prolonged high dosage has been continued for weeks or months, the dosage should be reduced gradually over a period of 1 to 2 weeks. Abrupt withdrawal may produce anxiety, anorexia, insomnia, vomiting, ataxia, tremors, muscle twitching, and rarely, epileptiform seizures. There seems to be evidence that meprobamate can produce a typical addiction pattern in high doses, especially in alcoholics and former narcotic addicts. Fatalities have been reported following accidental or intentional ingestion of meprobamate (Berger, 1963).

Meprobamate is administered orally in 200 or 400 mg. tablets. The dosage schedule varies from 1 to 6 tablets daily. The dose must be individualized to meet the patients' needs and prescribed in the smallest quantity, especially for patients who have suicidal or addiction tendencies.

**Phenaglycodol (Ultran).** Phenaglycodol has a "diol" chemical structure related to mephenesin and meprobamate. The latter drugs are propanediols, phenaglycodol is a butanediol as shown in the formula.



Phenaglycodol
(2-*p*-chlorophenyl-3-methyl-2,3-butanediol)

Phenaglycodol is a white crystalline powder which is nearly insoluble in water. It elicits anticonvulsive and sedative activity in rats. Doses of 55 to 80 mg./kg. administered intraperitoneally to mice evoke a reduction in spontaneous activity. Muscle weakness but no ataxia was evoked by phenaglycodol. Larger doses produce a loss of pinnal and righting reflex, but the corneal reflex is reported to remain brisk.

Phenaglycodol in intraperitoneal doses of 20 mg./kg. in cats causes a diminution in spontaneous movement. Monkeys receiving 50 to 100 mg./kg. by stomach tube become less aggressive and less fearful.

Phenaglycodol evokes a selective depressant action on polysynaptic pathways at the spinal and supra-spinal level. Thus, phenaglycodol shares this action with such drugs as mephenesin and meprobamate.

Phenaglycodol may be classified as a mild sedative with weak skeletal muscle relaxing properties. It is comparable to meprobamate.

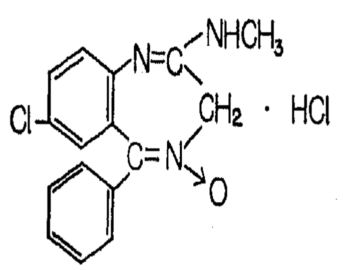
**Clinical use of phenaglycodol.** The principal use of phenaglycodol is for the production of a tranquilizing effect in anxiety-tension states. Its action is mild and rapidly effective. Emotional relaxation is achieved within 15 to 30 minutes after the administration of phenaglycodol.

From the comparative limited clinical experience with phenaglycodol at present it appears to be indicated in tension-anxiety states and in functional disorders. Further, like meprobamate, phenaglycodol is indicated in organic diseases in which anxiety is present. Phenaglycodol is of no value in psychotics. There are no contraindications or untoward effects which have come to our attention.

Phenaglycodol is given orally in capsules of 300 mg. The recommended dose is 300 mg., 3 or 4 times daily. Two capsules may be given before retiring, to promote sleep.

**Chlordiazepoxide (Librium).** This drug has sedative and muscle relaxant properties but only weak hypnotic effects in animals. It is 7-chloro-2-

methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride.



Chlordiazepoxide Hydrochloride

The hydrochloride salt is a colorless, crystalline material very soluble in water. It is unstable in solution and the powder must be protected from light.

Chlordiazepoxide depresses avoidance responding and spontaneous locomotor activity in rats. It has a calming effect on rats made irritable by lesions in the septal area of the brain, and it exerts a taming effect on monkeys and several kinds of wild animals removed from their native habitat. The drug has anticonvulsant activity against pentylenetetrazol and electroshock in mice. In rats chlordiazepoxide exhibits antiinflammatory activity similar to aminopyrine. It produces appetite stimulation in rats and dogs, (Randall *et al.* 1960).

**Clinical use of chlordiazepoxide.** Chlordiazepoxide has been used with some success in the treatment of mild anxiety, tension, and fear states when these are associated with organic diseases. Larger doses have been used with limited therapeutic value in more severe anxiety and tension states, agitated depression and severely disturbed psychotic patients.

A large number of uncontrolled clinical reports indicate that this drug will relieve anxiety, tension, and agitation associated with neuroses. The dose required to produce a calming effect does not elicit a marked degree of drowsiness or ataxia, although some elderly subjects have experienced these effects. The drug does not influence pathologic thought content as in phobias or obsessions; rather it produces an attitude of indifference. Its usefulness may be between the effectiveness of meprobamate and the phenothiazine drugs.

Chlordiazepoxide appears to be very effective in treating the acute symptoms of alcohol withdrawal syndromes. In chronic alcoholics the delirium tremens and agitation can be controlled by parenteral administration. Some reports on the value of this drug in treating these symptoms in this therapeutically difficult condition have been very enthusiastic.

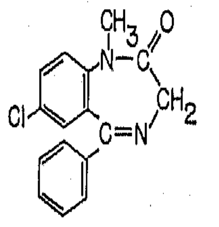
In mild to moderate anxiety and tension states the usual adult oral dose is 10 mg., 3 or 4 times daily. The smallest effective dose for each patient should be determined. Elderly or debilitated subjects may require only 10 to 20 mg. per day. In the treatment of the acute alcoholic syndrome 50 to 100 mg. is given intravenously or intramuscularly, but the total dose should not exceed 300 mg. daily.

Chlordiazepoxide is available as 5, 10, 25 mg. capsules and as a sterile powder for injection.

Chlordiazepoxide in some patients may produce drowsiness, ataxia, and lethergy. In elderly or debilitated patients syncope and incoordination may be associated with the usual adult doses. Episodes of rage, excitement, hostility, and severe depersonalization reactions may follow the administration of chlordiazepoxide to some schizophrenic patients. Extreme care must be exercised if this drug is given to patients with impaired renal or hepatic function. The administration of drugs known to potentiate the action of other agents, *e.g.*, monoamine oxidase inhibitors or phenothiazines, should be avoided when chlordiazepoxide is administered.

Chlordiazepoxide has been reported to cause skin rashes, nausea, headache, agranulocytosis, decreased tolerance to alcohol, and a change in libido. The drug should not be prescribed for patients who are prone to take excessive amounts of central nervous system depressants.

**Diazepam (Valium).** Diazepam is a benzodiazepine related to chlordiazepoxide, and its pharmacologic actions are qualitatively similar. It is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.



Diazepam

Diazepam is approximately 5 times as potent as chlordiazepoxide as a tranquilizer and skeletal muscle relaxant in animals. It exhibits anticonvulsive action against strychnine, pentylenetetrazole, or electroshock in mice. The drug produces skeletal muscle relaxation, reduces fighting in

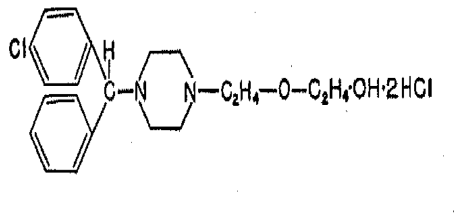
mice induced by electroshock, reduces decerebrate rigidity, and induces sedation and ataxia. Diazepam has a taming effect in monkeys similar to the response to chlordiazepoxide (Randall *et al.* 1961).

Diazepam is used in allaying anxiety and psychoneurotic states manifested by tension, fear, fatigue, and agitation. It may be of value in treating the muscle spasm associated with cerebral palsy and athetosis. It may also be useful in treating the acute agitation of alcohol withdrawal in chronic alcoholic patients. Diazepam is of no value in treating anxiety in psychotic patients, and its use should be avoided in these patients.

Diazepam is contraindicated in infants or patients with a history of convulsive disorders or glaucoma. It has the same limitations and precautions for use as does chlordiazepoxide. Concomittant administration of barbiturates, phenothiazines, MAO inhibitors, and other antidepressants should be avoided because these drugs may markedly enhance the action of diazepam. The simultaneous ingestion of alcohol will potentiate the action of diazepam. As with any new drug, prolonged administration requires periodic blood counts and liver function tests. Abrupt cessation of a high or prolonged dosage may precipitate the similar withdrawal pattern in patients observed with barbiturates, meprobamate, or chlordiazepoxide.

The usual oral adult dose of diazepam is 2 to 5 mg. 2 or 3 times daily. In severe psychoneurotic reactions the dose may be 5 to 10 mg. 3 or 4 times daily.

**Hydroxyzine Hydrochloride (Atarax, Vistaril).** Hydroxyzine is related chemically to some of the antihistaminic drugs. It has a pronounced effect upon the central nervous system. Its structure is shown in the following formula.



Hydroxyzine Hydrochloride
(1(-*p*-chlorobenzhydryl-)4-[2-(2-hydroxyethoxy)-ethyl]-piperazine dihydrochloride)

Hydroxyzine hydrochloride is a white crystalline powder which is soluble in water. Vistaril is the pamoate salt.

In animals hydroxyzine produces mild sedation without loss of reflex activity or lessened body movements. The animals remain in a reposed state until disturbed. Animals under the influence of hydroxyzine are still capable of responding with agility when stimulated. In the isolated guinea pig ileum preparation hydroxyzine elicits a powerful antispasmodic effect. This antispasmodic action can be demonstrated *in vivo* but, this action of the drug has not been useful clinically. Hydroxyzine also evokes coronary vasodilation and counteracts experimentally-induced cardiac arrhythmias. However, the drug has not been used therapeutically for the control of cardiac arrhythmias.

Hydroxyzine appears, from animal studies, to have a wide margin of safety. Its central nervous system effects suggest a mild sedating action without marked motor impairment.

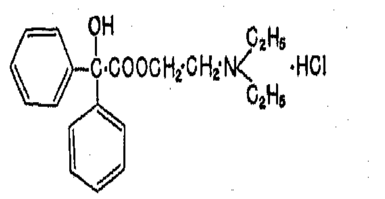
**Clinical use of hydroxyzine.** Hydroxyzine is recommended for the tense, anxious patient rather than for the psychotic person. Reports describing the use of hydroxyzine in anxiety states indicate its usefulness in these cases.

Hydroxyzine has been used in cases in which the patients exhibited mild to severe anxiety, melancholia, and hysteria. Psychotic patients and those with severe depression or hysteria do not benefit from hydroxyzine therapy.

The usual oral dose of hydroxyzine for adults is 25 mg. 3 or 4 times daily in tablets. The dose will vary with the severity of the symptoms and the response of the patient. *Vistaril* is a higher dosage form intended for more intensive medication.

Hydroxyzine in large doses produces side effects of excessive drowsiness, and the drug enhances the depressant effects of barbiturates and narcotic analgesics. Simultaneous dosage with these agents requires caution and a relatively lower dose of hydroxyzine. In general, the toxicity of hydroxyzine appears to be low, and the drug rarely causes undesirable reactions.

**Benactyzine Hydrochloride (Suavitil, Phobex).** Benactyzine is a diphenylmethane derivative as shown in the following formula:



Benactyzine Hydrochloride
(2-diethylaminoethyl benzilate hydrochloride)

Benactyzine hydrochloride is a white crystalline powder which is readily soluble in water.

Benactyzine is rapidly absorbed from the gastrointestinal tract of animals and readily excreted in the urine. The compound elicits strong anticholinergic activity. It also produces local anesthesia. On the heart, benactyzine evokes an antiarrhythmic action resembling quinidine. The action on the central nervous system is marked in that it diminishes the response to stress to which rats and cats are subjected.

Although the mechanism of action is unknown, it is obvious that benactyzine is not a depressant of the central nervous system similar to the other psycholeptics. Its marked anticholinergic action, about ¼ that of atropine, may be a factor in its use in psychoneurotic patients.

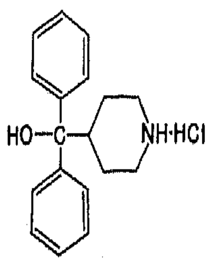
**Clinical use of benactyzine.** Benactyzine has been used in a series of mentally disturbed patients including schizophrenia, anxiety neurosis, endogenous depression, hysteria, and other related conditions. A regimen of 2 mg. of benactyzine 3 times a day produced no beneficial effects in patients with muscular rigidity, spasm, or pain. Flexor nocturnal spasms were diminished in some patients, enabling them to enjoy undisturbed sleep. The side effects were mainly psychological but serious since they involved increasing thought blockade, impairment of concentration, and clumsiness in task performances. These effects were encountered in a large segment of patients receiving 4 mg. of benactyzine 3 times a day.

Benactyzine is used in anxiety and tension states. Most reports indicate that about half of the patients will be improved by this drug therapy. A number of reports suggest that the benefits in psychotic patients are no greater than those obtained with placebo medication.

Benactyzine has the capacity of evoking a feeling of detachment or general apathy. Many patients describe it as a far away feeling that may amount to one of depersonalization.

The initial suggested oral dosage of benactyzine is 1 mg., 3 times daily. This may be increased to 3 mg., 3 times daily if improvement does not occur. The dose must be individualized and a total daily dose of more than 10 mg. is undesirable. Patients must be carefully observed for untoward effects. Benactyzine is contraindicated in patients with glaucoma, those who are extremely hostile, or those about to receive electroshock therapy.

**Azacyclonol, N.F. (Frenquel).** Azacyclonol is an isomer of pipradrol, page 479. Although these drugs are isomers, their pharmacologic responses elicited from the central nervous system are markedly different. Pipradrol increases the activity of laboratory animals; azacyclonol depresses their spontaneous activity.



Azacyclonol
(4-piperidyl diphenyl carbinol hydrochloride)

**Clinical use of azacyclonol.** Azacyclonol was first reported in 1955 as capable of antagonizing the syndromes of psychotic-like effects produced in man by the administration of LSD-25 or mescaline. In psychotic patients the results have been extremely variable. Some workers have used combined therapy of azacyclonol and chlorpromazine or reserpine in attempts to diminish mental confusion in schizophrenia with a hallucinogenic component. The results have been claimed to be superior to those achieved by any of the drugs alone.

Azacyclonol has been the subject of much controversy in the literature; some reports indicate that it is an effective drug; others have found it no more active than a placebo.

Although azacyclonol may have a limited place along with other drugs in psychiatry, at present its effectiveness is not clear. Favorable results may be related to adequate dosage or more critical diagnosis of candidates for therapy. The toxicity of the drug appears to be low, and large doses have not produced untoward side effects.

The adult oral dose of azacyclonol hydrochloride is from 20 to 100 mg., 3 times daily. Intravenous doses of 100 mg. may be administered every 8 hours for 1 to 7 days in the treatment of toxic pyschoses and delirium tremens. The dose must be adjusted for each patient.

### The Psychoanaleptic Drugs (Monoamine Oxidase Inhibitors)

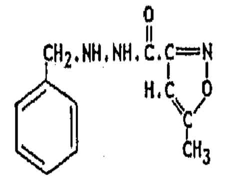
**Iproniazid (Marsilid).** Historically it was noted that when the drug iproniazid was first used in tuberculosis chemotherapy in 1952, it produced a marked central nervous system stimulation. Patients experienced an elevation of mood, increased vigor, and a resistance to fatigue.

Iproniazid and a number of chemically related compounds were discovered to be potent monoamine oxidase inhibitors. The significance of this fact was discussed previously in the consideration of the role of neurotransmitter substances in the central nervous system. These compounds increase the concentrations of serotonin and norepinephrine in the brains of animals. In addition, they antagonize reserpine-induced stupor in animals. In spite of extensive investigations of these actions, no causal relationship between monoamine oxidase (MAO) inhibition, serotonin or norepinephrine brain levels, and clinical effectiveness in depressed patients has been demonstrated.

Iproniazid is no longer used in therapy because it is too toxic. However, the discovery of this drug led to the synthesis of a large group of new drugs useful in the depressions; some are MAO inhibitors, and some do not elicit this action.

In general, since the place of the psychoanaleptic drugs remains to be established, the use of the monoamine oxidase inhibitors and other antidepressive agents in psychotic patients is essentially experimental in character. Numerous uncontrolled studies have reported favorable results following the use of these drugs in depressions. On the other hand, some controlled studies have not been able to show any significant differences between drug, placebo, and psychotherapy groups. To some degree, the confused picture that is presented by the conflicting clinical reports may be related to the extreme difficulty in reaching agreement on diagnostic categories in depressions. Some authors have referred to a favorable response by a patient on antidepressive drug therapy as a diagnostic sign.

**Isocarboxazid (Marplan).** Isocarboxazid is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine. It is a colorless, crystalline substance with very little taste, soluble in water to the extent of 0.05 per cent.



Isocarboxazid

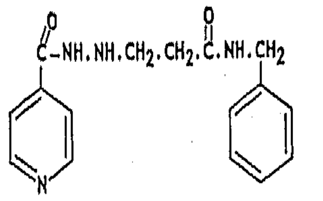
Isocarboxazid is more potent as an MAO inhibitor than iproniazid, when added to rat liver mitochondria, and 30 times more potent *in vivo* on the MAO activity in rat brain.

**Clinical use of isocarboxazid.** Isocarboxazid has been found to be effective in treating the depressed phases of anxiety, manic-depressive states, involutional, obsessive, and the disassociative reactions of psychotic disorders. Isocarboxazid has been reported to be more active than a placebo in relieving depression of mood and somatic preoccupation in many depressed patients. While adequate controlled comparable studies are lacking, isocarboxazid does not appear to be as effective as electroshock therapy in severe psychotic disorders.

The dosage must be adjusted to the individual needs of the patient. The usual initial oral dose is 30 mg. of isocarboxazid daily, in a single or in divided doses. It is not recommended that higher doses be employed routinely. When the therapeutic response has been established, a maintenance dose of 10 to 20 mg. daily, or less, should be administered. The patient must be observed carefully for toxic signs characteristic of these drugs. Its use should be discontinued at the first sign of jaundice or impaired liver function. Some patients may improve within a week or less of therapy, although others may require 3 to 4 weeks of treatment before improvement is noted. Because isocarboxazid has a cumulative effect, dosage should be reduced as soon as some degree of improvement in the patient is observed.

The untoward effects of isocarboxazid are characteristic of all the MAO inhibitors; *these must be watched for by the physician*, page 519.

**Nialamide (Niamid).** This drug is 1-(2-[benzylcarbamyl]ethyl)-2-isonicotinoylhydrazine. It is a white crystalline substance relatively poorly soluble in water (1.7 mg./ml.).



Nialamide

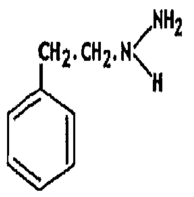
Nialamide is a monoamine oxidase inhibitor that is used in the treatment of psychotic and psychoneurotic depressions. In animals its action is equal to or more potent than iproniazid, depending on the species used. This drug is from 2 to 2.5 times more potent than iproniazid in potentiating the pyretogenic response of rabbits to intravenous injections of 5-hydroxytryptophan. It is less active than other MAO inhibitors in prolonging hexobarbital sleeping time. In the dog, nialamide does not cause hypotension when the body position is changed. In animals treated with nialamide, brain levels of serotonin and norepinephrine are increased as a result of MAO inhibition.

**Clinical use of nialamide.** Nialamide has been used in a variety of depressive syndromes, involving melancholia, postpartum depression, manic-depressive disease in the depressed stage, reactive depression, depressive symptomatology in schizophrenia, and psychoneurotic depression.

The initial dosage is 75 mg. daily as one dose or in divided doses. The dosage must be individualized. Since the pharmacologic response is delayed, each dosage must be administered for at least a week before revisions are made. Increases of 12.5 to 25 mg. are generally sufficient. Some patients, especially chronically depressed or regressed psychotics, may require substantially higher doses (up to 200 mg.). After a therapeutically satisfactory response is achieved, the dose should be reduced gradually. In some cases, doses as low as 12.5 mg. daily are adequate.

The same side effects of nervousness, insomnia, lethargy, vertigo, dry mouth, and jaundice, encountered after use of the other MAO inhibitors, have been reported following nialamide administration, page 519.

**Phenelzine Sulfate (Nardil).** Phenelzine is a potent monoamine oxidase inhibitor used as an antidepressive agent. It is $\beta$-phenylethyl hydrazine dihydrogen sulfate, a white, water-soluble powder.



Phenelzine

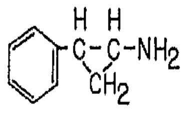
Intravenously in the cat and dog phenelzine elicits sympathomimetic effects producing a transient but marked pressor response, a contraction of the nictitating membrane, and dilated pupils. The drug does not produce significant blockade of the autonomic nervous system in these animals. It does not have marked spasmolytic action *in vitro* on the isolated guinea pig ileum. Phenelzine is said to preferentially inhibit MAO in the brain and to act to a lesser extent on liver MAO than iproniazid. The drug passes the blood-brain barrier readily. Mice, pretreated with phenelzine and then given reserpine immediately, or as long as 3 weeks later, become restless, hyperactive, and aggressive. Sedation is not produced.

**Clinical use of phenelzine.** Phenelzine is reported to produce beneficial effects in endogenous, essential, primary, or nonreactive depressions. The drug has also been used in the depressed phase of manic-depressive psychosis. Phenelzine is apparently most effective in recently hospitalized patients and those amublatory subjects with milder and less chronic depressions.

Only a few controlled studies have been made with phenelzine. Some workers have found ECT superior and others have reported endogenous depressions to respond favorably to the drug.

The adult oral dose is 15 mg., 3 times daily. The therapeutic effect is usually seen within 2 to 5 weeks. After satisfactory improvement is obtained, the dose should be slowly reduced to 15 mg., once a day. Dosage must be individualized, and careful observation of the patient is necessary. The toxic effects of phenelzine are the same as other MAO inhibitors, page 519.

**Tranylcypromine Sulfate (Parnate).** This MAO inhibitor is *trans-d,l*-2-phenylcyclopropylamine sulfate.



Tranylcypromine

This drug is not recommended for mild depressions. It is a nonhydrazine MAO inhibitor with unusually rapid action. In the symptomatic treatment of severe depressive states the drug may be effective more quickly than other antidepressive agents. The serious toxic effects of tranylcypromine severely limit its use.

The standard dosage recommended is approximately 20 mg. daily, adjusted in accordance with the patient's response. The details of the recommended dosage schedule must be followed very carefully to avoid serious or possibly lethal effects. *Under no circumstances should tranylcypromine be administered together with imipramine, amitriptyline or other MAO inhibitors.*

Paradoxical hypertension with severe headache, palpitation, neck stiffness, nausea, vomiting, sweating, and photophobia have been produced by tranylcypromine. Tachycardia or bradycardia with associated chest pain and dilated pupils may occur. Fatal intracranial hemorrhage has been reported. In addition, certain patients are particularly vulnerable to the effects of sympathomimetics in combination with tranylcypromine, and severe hypertension has been produced. The hazards of MAO inhibitors must be recognized with this drug.

The beneficial effects of tranylcypromine in severe reactive depressions, psychoneurotic depressive reactions, involutional melancholia, depressive phase of manic-depressive psychosis, and psychotic depressive reactions must be weighed against its dangers. Because less-toxic and equally effective drugs are available, the drug seems to have little justification for use in therapy.

**Toxicity and side effects of monoamine oxidase inhibitors.** Clinical experience has been limited with these relatively new drugs, and a number of years will be required before the potential usefulness and toxicity has been explored. In the interim, extreme caution in their use is required; close patient surveillance is demanded.

All the MAO inhibitors may produce headache, marked restlessness, insomnia, and postural hypotension. Some drugs of this class may induce hypertension. Hepatic toxicity and jaundice are relatively common toxic effects. Their cumulative action may have accounted for the high incidence of serious adverse reactions. The delayed action has led to improper high doses administered over a long time period. There are individual differences among the drugs of this group, but it is impossible at this time to determine which drugs are superior in terms of effectiveness and safety.

### THE PSYCHOANALEPTIC DRUGS (NON-MONOAMINE OXIDASE INHIBITORS)

These antidepressive agents are represented chiefly by imipramine and amitriptyline. Methylphenidate (Ritalin) is also used as a nonspecific central nervous system stimulant and is considered on page 479. Pipradrol (Meratran) is a weak psychic stimulant and it is discussed along with other nonspecific central nervous system stimulants on page 479. Deanol (Deaner) is presented in this section.

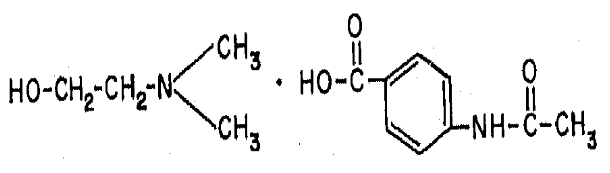
**Deanol, Acetamidobenzoate (Deaner).** Deanol is the *p*-acetamidobenzoic acid salt of 2-dimethylaminoethanol. It is a central nervous system stimulant used as a mild antidepressive agent.

Deanol was introduced as a compound that could serve as a source of acetylcholine in the body. The reports on its pharmacology have been conflicting. While the drug has central and peripheral actions and is capable of antagonizing the effects of barbiturates on the EEG, it may not be correct to ascribe these actions to the conversion of deanol to acetylcholine in the nervous system.

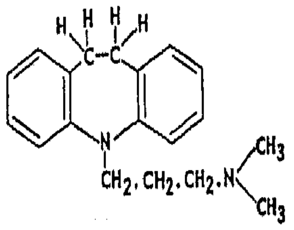
**Clinical use of deanol.** Deanol is a mild stimulant which has been reported to counteract lassitude, fatigue, depression, and oversedation. The most satisfactory results have been obtained with deanol in chronic fatigue and mild depression in the neurasthenic patient. Less satisfactory results have been obtained in institutionalized patients with severe depressions or agitated depressions. The appraisals of its effectiveness in mild depressions have ranged from the enthusiastic to the quite conservative. Deanol appears to have been most effective for the alleviation of the problem of shortened attention periods in children of school age with behavior problems and learning difficulties.

The adult oral dose of deanol is 50 mg. daily expressed in terms of the free base; the maintenance dose is from 25 to 100 mg. per day. For children over 6 years of age the initial dose may be 100 to 300 mg. per day with a maintenance dose of 75 to 150 mg. per day depending upon the degree of behavioral disturbance. The drug appears to have very few side effects. It is contraindicated in grand mal epilepsy and convulsive states.

**Imipramine (Tofranil)** can be considered as an isostere of promazine in which 2 $CH_2$ groups replace the sulfur atom in the phenothiazine ring. Chemically the compound is N-(3′-dimethylaminopropyl)-iminodibenzyl hydrochloride. It was first synthesized by Thiele and Holzinger in 1889.



Deanol



Imipramine

The hydrochloride salt is a white crystalline substance, turning yellowish or reddish on long exposure to light. It is soluble in water.

Imipramine is absorbed orally and is distributed to most body tissues including the brain. It dose not induce psychomotor agitation in the rabbit, cat, dog, rat, or mouse. Doses of 10 to 30 mg./kg. intraperitoneally produce sedation that is antagonized by central nervous system stimulants. Imipramine prolongs barbiturate sleeping time but is less potent in this respect than chlorpromazine. It protects mice against the tonic component of electroshock and pentamethylenetetrazol convulsions (Sigg 1959). In rabbits imipramine blocks the EEG arousal pattern reaction. This effect is synergized by chlorpromazine; reserpine on the other hand, antagonizes this action. Because imipramine augments the cortical responses of the EEG elicited by sciatic nerve stimulation, and convulsant spikes are recorded from the hippocampus and amygdaloid nucleus, it is contended that the drug acts as a stimulant.

Other pharmacologically interesting aspects of imipramine are its weak anticholinergic properties, vagal blocking action, transient hypotensive effect, and spasmolytic action. The blood pressure responses following administration of acetylcholine, histamine, and serotonin are diminished by imipramine. Epinephrine response is unchanged while the pressor effect of norepinephrine is enhanced and prolonged, although the mechanism is not through MAO inhibition. Imipramine may exert its antidepressant effect by sensitizing central adrenergic synapses (Sigg, 1959). The drug does not influence mono- or poly-synaptic spinal reflexes. The conditioned escape-avoidance response in the rat is not altered even by large doses of imipramine administered for long periods of time. The initial pharmacologic studies with imipramine did not suggest antidepressive action in man; indeed, its mode of action remains to be elucidated.

The drug is relatively nontoxic in experimental animals. The acute, oral $LD_{50}$ for the rat is 682 mg./kg. and approximately 175 mg./kg. in dogs. The clinical experiences with imipramine have indicated that the drug is well tolerated and serious side effects are rarely encountered.

The discovery of imipramine as a non-MAO inhibitor useful in depression indicates that MAO inhibition is not a prerequisite for antidepressant drug effect. Imipramine exerts an action on the peripheral adrenergic nervous system; its central action may be related to sensitization of central adrenergic synapses. Despite these pharmacologic differences, the clinical effects of imipramine and the MAO inhibitors are similar.

**Clinical use of imipramine.** Imipramine is indicated as specific for the treatment of depression. It has little effect on other psychotic or neurotic symptoms. It has been used successfully in psychomotor retardation, despondency, and the associated states of depression; in endogenous depression, involutional meloncholia, reactive depression, and the depressive phase of manic-depressive disease. In depression associated with organic disease, or in the aged, some caution is indicated since these patients are prone to develop severe neurologic symptoms on high dosage, and patients with severe cardiovascular disease are sensitive to the hypotensive effects of the drug. Approximately ⅔ of depressed patients respond favorably within 2 to 3 weeks.

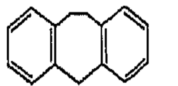
Although imipramine causes side effects of sweating, dry mouth, skin eruptions, tremor, and mild postural hypotension, it has rarely caused jaundice. It appears less likely to produce the serious effects of some of the MAO inhibitor antidepressive drugs.

The dose of imipramine must be determined on an individual basis for each patient. In hospitalized patients an initial daily divided, dose of 100 mg. is recommended, administered either orally or intramuscularly. This may be increased by 25 mg. every few days, depending on tolerance, up to 200 mg. daily. If necessary, after 2 weeks of this dosage, the amount may be increased to 250 to 300 mg. daily, preferably, with part of the dose given intramuscularly.

In outpatients, an initial dose of 75 mg. is advised. This may be increased to 150 mg., daily. A dose exceeding 200 mg. daily, is not recommended for outpatients. A lag of a few days to a few weeks in the therapeutic response, occurs at the onset of therapy. This is not likely shortened by increasing the dose and initial high doses may increase the incidence of side effects. After the response becomes evident, the dosage may be reduced gradually to from 50 to 150 mg., daily.

The drug should be used with caution in patients with an increased intraocular pressure. In general, it appears that this drug is the safest antidepressive agent available, suitable for use in treating the majority of cases of depression irrespective of their precise diagnostic classification.

**Amitriptyline (Elavil).** Amitriptyline is closely related chemically to imipramine. It is 10,11-dihydro-N,N-dimethyl-5H-dibenzo [a,d] cycloheptane-$\Delta^5$,$\gamma$-propylamine hydrochloride.



Amitriptyline

Amitriptyline elicits a marked effect upon the central nervous system of animals, and it has a variety of pharmacologic actions. Its structural similarity to imipramine and the substituted phenothiazines that also cause these responses makes this drug of considerable theoretical interest. In cats amitriptyline produces a slowing of spontaneous electrical activity of the brain, and the brain wave pattern resembles that seen in states of sedation. This action seems to be selective for the alerting mechanism, because stimuli such as auditory clicks or light flashes produce specific cortical potentials in a normal manner.

Only large doses of amitryptyline produce a reduction in the rate of avoidance responding in rats to shock. Their ability to escape the noxious stimulus is not impaired.

Amitriptyline prolongs barbiturate-induced anesthesia in mice. The drug alone does not cause appreciable sedation in mice in low doses of 10 mg./kg. It blocks the depressor responses of histamine, antagonizes the bronchial spasm of histamine in guinea pigs and the isolated ileum preparation. Its antihistaminic potency is approximately equal to chlorpheniramine.

Amitriptyline shows mild anticholinergic activity against acetylcholine and vagal stimulation in dogs. An intravenous dose of 6 mg./kg. produces only minor blockade of epinephrine. Its actions in man do not seem to be referable to adrenergic blockade. The oral $LD_{50}$ in mice is 280 mg./kg. Intravenously the $LD_{50}$ is 29 mg./kg.

**Clinical use of amitriptyline.** Amitriptyline is a mild tranquilizing antidepressive agent. It is not a monoamine oxidase inhibitor, and the drug therapeutically closely resembles imipramine. If is used in the treatment of the depressed phases of anxiety and manic-depressive states and in involutional melancholia. Its value in treating the depressed schizophrenic patient is often obscured by aggravation of the schizophrenia. In neurotic depressive reactions amitriptyline may be less effective than imipramine. Because the drug has been available for use only a short time and the reported controlled studies are few, it is difficult to assess the place of amitriptyline in treating depressive psychiatric disorders.

Amitriptyline, like imipramine, rarely elicits excitement or stimulation, but it may produce sedation. The incidence of adverse reactions following amitriptyline administration is low. These side effects have been xerostomia, tremor, weakness, blurring of vision, constipation, urinary retention, drowsiness, fatigue, anorexia, epigastric distress, nausea, and vomiting. More disturbing reactions have been edema, tachycardia, orthostatic hypotension, excessive perspiration, and tingling of the arms. Epileptiform convulsions have been reported in some chronic schizophrenic patients following intensive therapy. Most of these untoward effects are relieved when the drug is discontinued or the dose is reduced. A few cases of skin rash have been observed. Although serious toxic effects have not been reported, the patient receiving this drug should be supervised closely. Concomitant therapy with other drugs, *e.g.*, barbiturates are contraindicated and *MAO inhibitors must not be administered to these patients.*

The adult oral dosage schedule of amitriptyline is 75 mg. daily initially in divided doses. The dose may be increased in daily increments of 25 mg. up to a total daily dosage of 150 mg. for non-hospitalized patients. A few hospitalized patients may safely be given a daily dose of 300 mg. to achieve a satisfactory clinical response. The antidepressive effects may not be observed until the drug has been administered for 4 to 10 days, and some patients may not experience therapeutic benefit until the medication has been given for 4 to 6 weeks. The individual dosage schedule must be selected and maintained throughout the depressive phase of the illness.

### Shock Therapy in Psychotic States

**Electroshock therapy.** Electroshock therapy (EST) was probably the most significant technic developed in the treatment of mentally disturbed patients in a half-century prior to the use of the psychotropic drugs. These drugs have not displaced its use; they have supplemented it and broadened the spectrum of effective treatment. It is considered the treatment of choice by many for most cases of *involutional psychotic depressive reactions*. It is especially useful in reducing the time period required to tranquilize over-active and agitated patients. The mechanism of response to this treatment procedure remains obscure, yet there are some interesting hypotheses that have been formulated correlating the results of this procedure with the action of the pyschotropic drugs.

It has been proposed that electroshock treatment ameliorates the secondary traumatic state of the ego such as panic and/or depression by reducing the excitability of the cerebral cortex. Therefore, unconscious (subcortical, norepinephrine-precipitable) warning anxiety can no longer break through and overstimulate the ego into panic or depression. Thus, the defense of the ego is increased by electroshock therapy and partially insulated against subcortical noxious stimuli. The psychotropic drugs, such as chlorpromazine, diminish the primary unconscious, subcortical, norepinephrine-precipitable anxiety which induces panic and/or depression if projected to the cerebral cortex. Thus, these drugs find use in relieving agitation and overactivity, especially manic psychoses in which the secondary effects of disorganization of the ego are slight or reversible. Other views have been expressed regarding the mechanism of electroshock in mitigating the symptoms of endogenous depression. Some workers contend that electroshock therapy destroys the tendency of the endogenous depression to become fixed. The sequence of shock treatments is important, and psychotherapy is essential to prevent a prompt relapse.

**Insulin shock treatment.** Sakel in 1929 introduced insulin shock treatment for schizophrenia. It may be used combined with electroshock and the psychotropic drugs. In the early days of insulin shock therapy, Sakel considered it a specific for schizophrenia. Now it is not considered a specific treatment for schizophrenia.

The mechanism of action of the beneficial effect of insulin shock treatment in schizophrenia is not known. Simultaneous psychotropic drug therapy is not interdicted. Indeed, it appears to be completely compatible with insulin shock therapy and is very useful in tranquilizing overactive and agitated schizophrenics.

Several controlled studies have been made comparing insulin coma therapy and chlorpromazine therapy. Insulin coma therapy could not be shown to be superior to chlorpromazine administration. An occasional patient may respond to insulin shock treatment after failing to respond to drug therapy or EST; however, many institutions find it difficult to justify maintenance of a unit to provide a therapy that is as expensive and occasionally hazardous as the insulin coma treatment.

**Hexafluorodiethyl ether (Indoklon) convulsive therapy.** A new pharmaco-convulsive agent, hexafluorodiethyl ether (Indoklon) was studied by Krantz *et al.* (1959). This substance is a volatile liquid and was one of the many agents studied by the authors for possible anesthetic properties. The composition of hexafluorodiethyl ether is shown in the following formula:

$$CF_3CH_2—O—CH_2CF_3$$

The convulsions elicited by the inhalation of hexafluorodiethyl ether in various laboratory animals strikingly resembled the seizure produced by electroshock therapy. This prompted the use of this volatile agent in the treatment of mentally ill patients. The agent is administered by inhalation in an especially designed anesthetic mask. The inhalation of 0.5 to 1 ml. of the drug in the form of a vapor induces a grand mal type of seizure within 30 seconds. There is a very short period of apnea which automatically terminates the inhalation of the drug. Unconsciousness supervenes prior to the convulsive seizure. Recovery is prompt and uneventful.

This type of convulsive therapy has been used by Kurland and his associates (1957 et seq.) and others (1963) in thousands of treatments. Its therapeutic value appears to be tantamount to that of electroconvulsive therapy. It was observed that the majority of patients experienced less apprehension, and the inhalation of a vapor was less threatening than the concept of an electric shock. It has been revealed that certain mental patients who did not respond to EST responded well to hexafluorodiethyl therapy. There also appears to be evidence that hexafluorodiethyl ether therapy is more successful in schizophrenia than EST. The untoward effects observed appeared to be similar to those frequently encountered after electroconvulsive therapy but symptoms disappear rapidly.

Further studies of the pharmacologic action of hexafluorodiethyl ether revealed that the seizures were compatible with atropine, thiopental sodium, and succinylcholine chloride premedication. In the rat the threshold seizure time and the dose of the hexafluorodiethyl ether are not significantly affected by premedication with iproniazid or prochlorperazine. It is reduced by reserpine and high dosage levels of chlorpromazine. In the anesthetized dog and monkey, hexafluorodiethyl ether evokes central stimulation of the respiratory rate and tidal volume without cardiac irregularities, (Ling *et al.* 1959).

Sustained exposure of dogs and monkeys to the vapor of hexafluorodiethyl ether for 30 minutes, 3 times a week, for 4 weeks, with the repetitious tonic-clonic seizures and the comatose state, did not appear to produce demonstrable damage to the nervous system that is revealed by histologic examination. Electrocardiographic studies, liver function tests, and blood and urine studies were negative (Krantz *et al.* (1959).

To simplify the treatment procedure, intravenous administration of hexafluorodiethyl ether was explored. A 10 per cent by volume solution of the agent was prepared and found to be satisfactory for intravenous use in animals and man. The effects resemble in all respects the results obtained by inhalation (Krantz *et al.* 1959).

Karliner and Padula (1962 *et seq.*) have used hexafluorodiethyl ether intravenously in therapy as a convulsive agent. They found the drug equally as effective as electroshock therapy in treating depressions and superior in schizoaffective disorders and in paranoid schizophrenics. They report that the agent, when injected as a 10 per cent solution, is a powerful and safe pharmacoconvulsive substance. The technic is simple and readily adapted to the hospital routine. According to these workers and Impastato (1960 *et seq.*), some patients prefer the intravenous route to the inhalation of hexafluorodiethyl ether. Fewer prolonged and secondary convulsions can be expected to follow intravenous dosage. The dose is modified according to the individual patient's response, but a very small amount is injected, usually 6 to 8 ml. of the 10 per cent solution. The clinical results parallel those obtained after EST. The newer methods of administration and combined use with skeletal muscle relaxing agents have demonstrated that the agent is safe and easy to administer. The potentialities of the drug will be uncovered in the near future.

## Drug Therapy in Mental Disease

It is doubtful whether or not the organic concept of mental disease modifiable by drugs can be accepted in its entirety to the exclusion of the psychodynamics involved. Of all the organs of the body, the brain alone has the capacity to be modified by past experience. This organ cannot escape the impact of reality involving the influence of other people, the inanimate world, and one's own inherited and acquired personality. The response to psychopharmacologic agents is the result of the interaction of the brain as an intricate and complex chemical system with the drug, but one which is also modified by the patient's personality and his environment. In our search, therefore, for better psychopharmacologic agents the psychodynamics of the patient's individuality should never be neglected.

Let us not delude ourselves that the innovation of drug therapy has checked the forces which stir the troubled waters of mental illness. They have only given us an oil to quell them. The effectiveness of intensive drug therapy is well established in the acute psychoses, and the phenothiazine drugs will facilitate the remission of symptoms in a significant number of patients. However, as has been pointed out by Cole and others (1960), even before these drugs were available, active treatment centers were discharging over 50 per cent of their newly admitted psychotic patients. Therefore, in evaluating the effectiveness of drug therapy comparative studies are necessary. New problems have been created by the use of drug therapy, social rehabilitation of large numbers of patients, and maintenance of drug therapy during integration of the patient into the community are now more pressing aspects of the treatment of the mentally ill.

One questions the wisdom of drug-induced tranquilization in many individuals, where drive and ambition, coupled with its associated tension, are the dynamic forces of their very existence. Their peace of mind is not tranquility, but achievement. To others, peace of mind may be acquired only by a tranquil state of inaction and irresolution. The physician has now in his hands a new set of tools, the psychotropic drugs. He must not use them without discrimination. What their name implies "peace of mind" is the goal for which all mankind has sought. Among the patients seeking the physician's help, talent and wealth are frequent attributes, fame and beauty are not uncommon, but peace of mind is often lacking, it is the final seal of divine approval; the endorsement of a well integrated life.

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# PART V

## THE RESPONSE OF THE AUTONOMIC NERVOUS SYSTEM TO DRUGS

# 33

# *The Autonomic Nervous System. General Considerations*

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The autonomic nervous system may be conveniently subdivided into the *parasympathetic* and the *sympathetic* divisions. This subdivision of the visceral nervous system is based upon the *anatomic origin* of the nerves, their *physiologic functions*, and their respective *pharmacologic responses to drugs*.

Anatomically the parasympathetic nerves originate at three different levels in the central nervous axis, *i.e.*, the midbrain, the medulla oblongata, and the sacral portion of the spinal cord. The sympathetic nerves have their origin in the thoraco-lumbar segments of the spinal cord Each division of the autonomic nervous system is composed of two neurons, namely, the presynaptic and the postsynaptic. In the sympathetic division the synapses between the pre- and postganglionic fibers are located in the vertebral and prevertebral ganglia. In the parasympathetic division the synapses are found close to or within the organ which the neurons innervate. The presynaptic fibers are myelinated or lightly myelinated, and the postsynaptic fibers are generally nonmyelinated.

Generally speaking, the visceral organs are innervated by sympathetic and parasympathetic fibers. The innervations are reciprocating in the same viscus. The parasympathetic system is usually involved in local reflexes. The sympathetic system, on the other hand, is more frequently involved in generalized mass reflex action.

In states of physiologic stress, widespread sympathetic discharge leads to changes in the body that anticipate or ameliorate the changes. This fact was described by Cannon as the emergency function of the sympathoadrenal system. As important as the sympathetic system is in preserving homeostasis in the body, it is possible for a sympathectomized cat to live for many months without apparent difficulty. The somatic nervous system is concerned with the adjustment of the organism to its environment. The autonomic nervous system is concerned with the internal adjustment of the organism to provide a *homeostasis* for the maintenance of all metabolic changes responsible for life. Thus the autonomic nervous system is involved with hormonal secretion, such as that of epinephrine and norepinephrine by sympathetic discharge and that of acetylcholine through parasympathetic discharge.

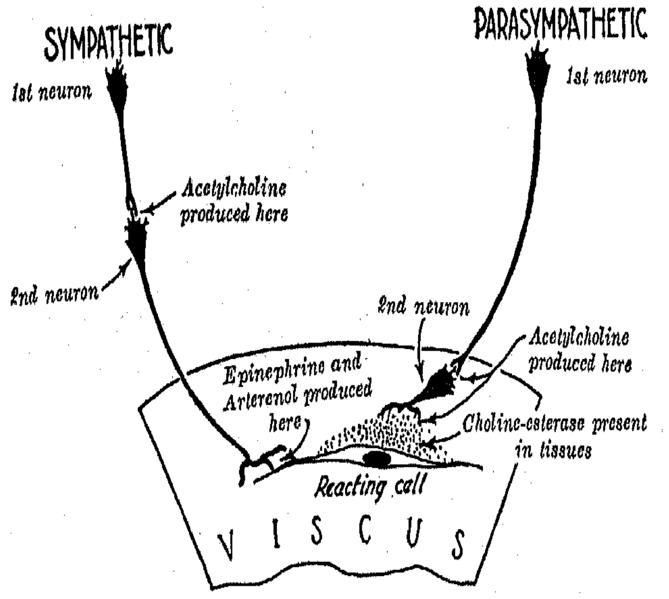
When somatic nerves to skeletal muscle are severed, the muscle undergoes degeneration and atrophy. Viscera which are innervated by sympathetic and parasympathetic fibers essentially remain functionally and anatomically unaltered by the severance of their autonomic innervation. In fact, these structures appear to develop a hypersensitivity to the hormones which are liberated when the fibers are stimulated. Thus the structure innervated by the sympathetic fibers becomes more active under the influence of epinephrine, and that innervated by parasympathetic fibers becomes more sensitive to acetylcholine.

### Cholinergic and adrenergic fibers.

The transmission of the nerve impulse from the pre- to the postsynaptic fiber is accomplished by the discharge of acetylcholine at the synapse. Thus acetylcholine plays a role of paramount importance in both divisions of the autonomic nervous system. In the parasympathetic division, the postsynaptic fibers initiate their response in the effector cells of the innervated organ by the liberation of acetylcholine on these target cells. These postsynaptic fibers are therefore called *cholinergic* fibers. In the sympathetic division the postsynaptic fibers elicit their response in the effector cells of the innervated organ by the liberation of epinephrine and norepinephrine on these target cells. These postsynaptic fibers are therefore called *adrenergic* fibers.

The roles played by acetylcholine and epinephrine in the autonomic nervous system are illustrated in figure 33-1.

The origin of the autonomic nerves and the organs innervated by them are shown diagrammatically in figure 33-2. It will be observed that there are cholinergic fibers which originate in the sympathetic division such as the fibers to the sweat glands.



SYMPATHETIC
1st neuron
Acetylcholine produced here
2nd neuron
PARASYMPATHETIC
1st neuron
2nd neuron
Acetylcholine produced here
Epinephrine and Arterenol produced here
Choline-esterase present in tissues
Reacting cell
V I S C U S

FIG. 33-1. The role of acetylcholine and epinephrine in the autonomic nervous system. (Modified from A. Myerson, J.A.M.A., 110: 101, 1938.)

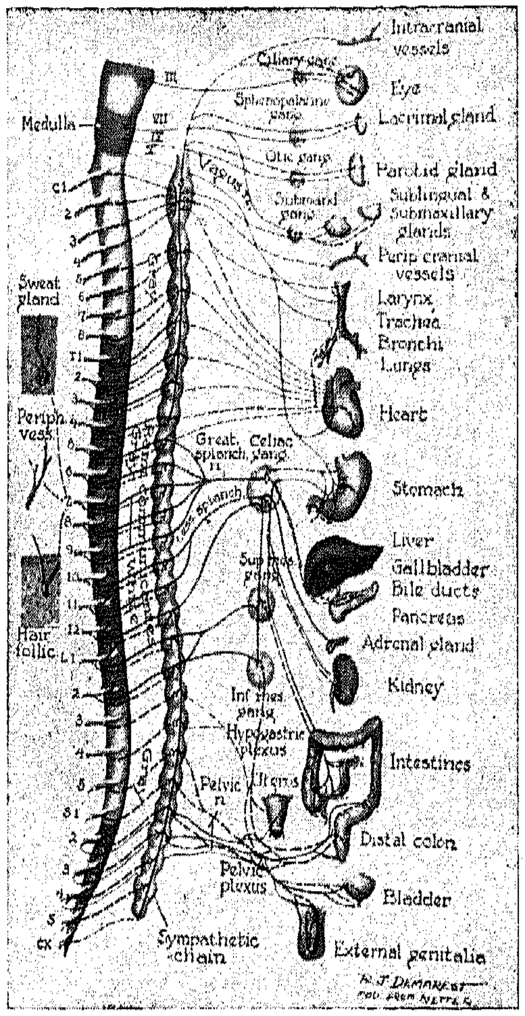


Fig. 33-2. Diagram of the autonomic nervous system. (From S. W. Ranson, and S. L. Clark, *Anatomy of the Nervous System*, Ed. 10. W. B. Saunders Company, Philadelphia, 1959.)

**Response to acetylcholine.**

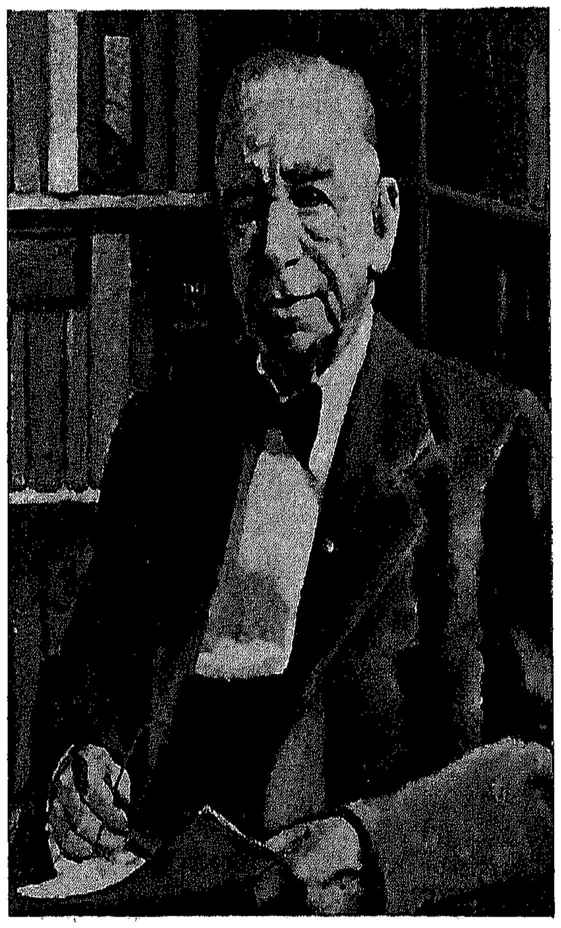
From the foregoing discussion and figures it is observed that acetylcholine is the substance which plays the major role in the functioning of the autonomic nervous system. Acetylcholine elicits 3 outstanding responses when administered to man or laboratory animals. They are:

1. Cardiac inhibition
2. Peripheral vasodilatation
3. Contraction of skeletal muscle

By the stimulation of the vagus the cardiac inhibitory effect of acetylcholine is produced. The classical experiments of Loewi (1921–1926) showed that the cardiac inhibition was due to the discharge of acetylcholine upon the target effector cells in the heart. He perfused a frog's heart with a Ringer's solution perfusate from another frog in which cardiac inhibition had been produced by vagal stimulation. The heart of the second frog was inhibited. Later this "Vagusstoff" was shown to be acetylcholine.

Bülbring and Burn (1949 *et seq.*) showed that acetylcholine formation is closely associated with the maintenance of cardiac rhythm. They observed that acetylcholine will elicit beating in the isolated rabbit atria when they have stopped functioning. Acetylcholine will also augment their rate and amplitude of beat. Furthermore, the activity of the isolated atria parallels their power to acetylate choline.

Armitage *et al.* (1957) showed that acetylcholine enhances the production of experimental atrial fibrillation, presumably by accelerating the return of potassium ions into the cells and thereby shortening the refractory period. Mazel and Holland (1958) studied the distribution of acetylcholine in the sinuses, atria, and ventricles of the frog and turtle hearts. The area of highest intrinsic rhythm (sinus) contained greater amounts of acetylcholine, true cholinesterase, choline acetylase, and sodium. Each of these concentrations was smaller in the areas of lower intrinsic rhythm. Of special interest is their observation that $Na^+:K^+$ ratio of the sinus was about twice that of the atria and about 3 times that of the ventricles.



OTTO LOEWI

*Recipient of the Nobel Prize in Physiology and Medicine*

"I named this substance 'Vagusstoff' and later on I was able to demonstrate that it was in all probability identical with acetylcholin, whose extreme efficacy, as you know, had first been demonstrated by Reid Hunt."

Cranefield *et al.* (1959) studied the action of acetylcholine on atrioventricular (A-V) nodal fibers, using intracellular microelectrodes. They observed that the application of acetylcholine produced characteristic changes in the action potentials of fibers in the atrial margin of the A-V node. Depolarization was retarded, the amplitude was reduced, and notching and slurring appeared in the upstrokes of the recording.

The glycogenolytic effect of epinephrine on the perfused heart of the guinea pig is completely blocked by acetylcholine. This action is independent of the negative chronotropic action of acetylcholine. Anoxic glycogenolysis in the atria was significantly inhibited by acetylcholine, but the effect upon anoxic glycogenolysis in the ventricles was slight (Vincent and Ellis, 1963). This interesting study shows further the multifaceted role of acetylcholine in cardiac metabolism.

Evidence is accumulating from many sources to indicate the importance of acetylcholine as an essential cellular constituent of cardiac tissue affecting cationic exchange and rhythmicity.

Evidence has accumulated that acetylcholine plays an important role in cellular metabolism, in addition to its activity as a neurohormone. The denervation of an organ innervated by cholinergic nerves increases the sensitivity of the organ to the action of acetylcholine. Welsh (1954) demonstrated that acetylcholine is involved in the growth and tissue maintenance in *planaria*. It has been shown that acetylcholine may be the substance required for the regeneration of the amputated *Triturus* limbs. Since this neurohormone is capable of changing the membrane potential of cells and the permeability of their membranes, it is likely that it plays an important role in their cellular metabolism.

One of the most effective antagonists to the action of acetylcholine is the belladonna alkaloid atropine. It must be emphasized that all of the responses to acetylcholine are not obliterated by atropine. The cardiac slowing produced by acetylcholine is completely abolished by atropine. Likewise, the second major response to acetylcholine, namely, peripheral vasodilatation, is effectively combated by atropine. However, the contraction of skeletal musculature (the somatic myoneural junction response of acetylcholine) is not antagonized by atropine. Neither peripheral vasodilatation nor skeletal muscle contraction is produced by vagal stimulation.

From the foregoing statement one learns immediately that the stimulation of a cholinergic nerve (vagus) does not give the complete pharmacologic syndrome produced by acetylcholine. Furthermore, when one speaks of a drug antagonist to a compound like acetylcholine it is important to consider the structure on which the antagonism occurs, for it has been shown that the autonomic action of acetylcholine at the neuromuscular junction of cholinergic fibers is blocked by atropine, but not its effect on the neuromuscular junction of somatic nerves.

Dale *et al.* (1936) offered an explanation for the failure of atropine to intervene at the myoneural junction of somatic nerves. He states: "The nerve impulses liberate acetylcholine so close to the reactive structures that atropine cannot intervene." In other words, Dale contends that the close anatomic relationship existing between the nerve endings and the effector cells in the somatic nerves blocks the atropine intervention. In the autonomic cholinergic innervations the anatomic structure at the neuromuscular junction is of such a character as to permit ready access to atropine.

The synaptic transmission of the nerve impulse is probably the result of the release of the chemical transmitter acetylcholine from the synaptic vesicles of the terminals of the presynaptic fibers. The transmitter must traverse the synaptic cleft and exert a depolarizing influence on the postsynaptic membrane. Further validity is added to the concept with the evidence that synaptic membranes are electrically excitable. Eccles (1959) proposes that where the pre- and postjunctional cells are closely opposed, ephaptic transmission occurs. Chemical transmission is required where the cells are separated by a synaptic cleft.

The action potentials of the postsynaptic fibers, which result from the stimulation of the presynaptic fibers, may be used as a measure of transmission of the nerve impulse across the synapse. Marrazzi (1939 *et seq.*) observed that cholinergic drugs such as pilocarpine facilitated the transmission across the synapse. Atropine exhibited an opposite effect. These observations lend credence to the concept that autonomic ganglionic transmission is mediated by acetylcholine.

Since the acetylcholine receptor sites are not the same at all loci where acetylcholine response is elicited, it would follow that to block its action at different structures, blocking agents of different structures are required. For example, at neuromuscular junctions *d*-tubocurarine is an effective blocking agent for acetylcholine, but not at autonomic ganglia. On the other hand, hexamethonium chloride is a blocking agent for acetylcholine at autonomic ganglia, but not at neuromuscular junctions. Thus at each receptor site the chemical configuration of the blocking agent for acetylcholine must fit with specificity to achieve an effective blockade. Chemical blocking agents of the autonomic ganglia, such as previously mentioned hexamethonium, do not inhibit the release of acetylcholine from the presynaptic nerve terminals. They do, however, enter into competitive inhibition with the acetylcholine released at this locus. These blocking agents differ in their response from nicotine and acetylcholine itself, inasmuch as they do not elicit initial depolarization and stimulation prior to blockade. In this respect the action of hexamethonium at the autonomic ganglia is similar to that of *d*-tubocurarine at the neuromuscular junction.

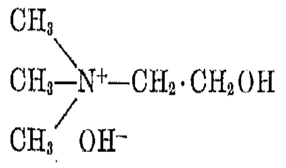
The smooth and skeletal muscle-stimulating activity of acetylcholine is most interestingly shown in the gastrointestinal tract of a primitive fish known as the *tench*. The intestinal coat of the fish is composed of an outer layer of skeletal muscle and an inner layer of smooth muscle. Each layer is innervated by the vagus. When the vagus is stimulated, or when acetylcholine is injected, both types of musculature undergo their characteristic contractions. After atropine, vagal stimulation or acetylcholine will produce an effect only on the outer coat of striated muscle. After curare, vagal stimulation or acetylcholine produces an effect only on the inner coat of smooth muscle because curare blocks the nerve impulse at the neuromuscular junction of striated muscle. When curare and atropine are administered, neither vagal stimulation nor acetylcholine causes any contraction in the gut of the tench because each action of acetylcholine has been blocked.

The action of acetylcholine in eliciting skeletal muscle contraction and on autonomic ganglia is referred to as the "nicotinic" action of acetylcholine. Its action on smooth muscle emulates that of the alkaloid *muscarine* and is referred to as a "muscarinic" action.

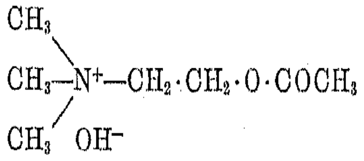
The nicotinic action of acetylcholine does not appear to be dependent upon the acetyl group in the molecule. Chang and Gaddum (1933) demonstrated that there was no loss in nicotinic activity when the acetyl group was removed from the molecule. Thus it was shown that propionylcholine is 2 to 5 times more active than acetylcholine in its nicotinic action. On the other hand, acetylcholine is 28 times more active than propionylcholine in reducing the blood pressure (muscarinic action).

### Choline and acetylcholine.

Choline is a ubiquitous substance found in most animal and many plant cells. When injected, choline, like acetylcholine, produces a fall in blood pressure. Hunt and Taveau (1906) isolated acetylcholine from the adrenal glands and showed that this acetylated choline derivative was from 10,000 to 100,000 times more active than choline itself. The structures of the two compounds may be seen in the formulas below.



Choline



Acetylcholine

### Mechanism of action of acetylcholine.

If acetylcholine is perfused into the vessels of a beating amphibian heart, its action in slowing the beat occurs within 1 second of contact (Welsh, 1955). It is likely, therefore, that the action is at or near the surface of the cell. From a consideration of the vast number of analogs and homologs of acetylcholine that have been studied pharmacologically, it is clear that a molecular structure which will fit into the cell receptors similar to those of acetylcholine is necessary to evoke response. For example, Welsh and Taub (1953), using the *Venus* heart (*Venus mercenaria*) showed that acetylcholine is 10,000 times more active than tetramethylammonium. By increasing the length of one of the methyl groups in tetramethylammonium to amyl, its activity with respect to acetylcholine increased to 1:70. Higher homologs were less active. Thus the maximal activity was achieved when the carbon chain was closest in length to that of acetylcholine, as illustrated in the formulas.

$$(CH_3)_3N^+CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_3$$

Amyltrimethylammonium

$$(CH_3)_3N^+CH_2\cdot CH_2\cdot O\cdot CO\cdot CH_3$$

Acetylcholine

It is clear from the formulas that the difference lies in the O·CO group. This group must play a role in the effective attachment of the molecule to the receptor site in the cell surface. This may occur through *van der Waals' forces* and through *hydrogen bonding*.

To lend further support to the "exactness of fit" hypothesis, the position of the carbonyl group is of striking importance. Thus if the carbonyl group is separated from the quaternary nitrogen atom by 3 ($CH_2$) groups, as in 4-ketoamyltrimethylammonium, the compound is devoid of acetylcholine-like activity on the blood pressure.

The precise nature of the acetylcholine receptor substance is not known. Welsh (1949) suggested that perhaps it is an enzyme which requires acetylcholine as its substrate for activation. Again, it has been postulated that acetylcholine may enter into competitive displacement on the cell surface with molecules of a similar chemical configuration. Danielli (1950) considers the key molecule to be in the lipid film. For example, lecithin is choline esterified with phosphoric acid linked to a long chain fatty acid. Thus the strongly polar choline portion of the lecithin molecule essential to the matrix of the cell surface might be displaced by acetylcholine. This could initiate local polarization changes, alter the selectivity of the membrane to ions, and elicit activity. Since the cardiac inhibitory effect of acetylcholine can be evoked by dilutions as low as $10^{-10}$ M, when applied to the surface of the *Venus* heart, it is clear that the agent attacks the vital receptive mechanism of the cell. The concept of acetylcholine's adsorption to the receptor surface of the cell is shown in figure 33–1.

### Depressor response to acetylcholine.

Acetylcholine and choline each produce a characteristic depressor response in the dog upon intravenous injection. The response to acetylcholine is elicited by 0.01 μg.; choline requires at least 1000 times this dose. Each response is peripheral in character and is blocked by atropine.

If one injects neostigmine, which inactivates cholinesterase, into the atropinized animal and then injects acetylcholine, the latter drug causes a rise in blood pressure. Choline elicits no response.

The rise in blood pressure produced by acetylcholine is due to its stimulating effect on autonomic ganglia. This is generally masked by its peripheral vasodilator action. But in the atropinized animals the peripheral response is blocked and the ganglionic action becomes manifest.

To support the view that the rise in blood pressure evoked by acetylcholine is due to its ganglionic action, the following experiment is of interest. In the atropinized, neostigminized, nicotinized animal, acetylcholine does not elicit a pressor response. Nicotine first stimulates, then paralyzes all autonomic ganglia, and after a blocking ganglionic dose of nicotine the target cells for the pressor response of acetylcholine are no longer available for the stimulating action of the compound.

One may pose the hypothesis that acetylcholine produces its pressor response in the atropinized, neostigminized dog by causing a discharge of epinephrine from the adrenal glands. However, in the animal treated with atropine and neostigmine with the blood vessels to the adrenals ligated, acetylcholine elicits a pressor action.

The sympathetic ganglia supply the postsynaptic fibers which are constrictor to the arterioles. The response is initiated on the effector cells in the arterioles by the discharge of epinephrine and norepinephrine at the neuromuscular junction of the adrenergic fibers. This is blocked by ergotamine. Therefore one is able to establish further the locus of action of acetylcholine by injecting the compound in the (1) atropinized, (2) neostigminized, (3) ergotaminized dog. In this animal acetylcholine no longer serves as a pressor drug. It stimulates the unaffected sympathetic ganglia motor to the arterioles, and at the neuromuscular junction epinephrine and norepinephrine are released, but their action is blocked at this point by ergotamine.

### Cholinesterase.

In the foregoing studies of the action of acetylcholine on the blood pressure, reference was made to the use of neostigmine. Neostigmine prolongs the action of acetylcholine and prevents its rapid destruction at the effector cells by *cholinesterase.* Cholinesterase is a specific enzyme present in blood and tissues which deacetylates acetylcholine. After this action the activity of the compound drops to only a minute fraction of its former potency. Thus a refractory period of synapse transmission or nerve to muscle conduction is established. At any autonomic ganglia like the cervical sympathetic, there is available sufficient acetylcholine for about 2000 synaptic transmissions. The esterase present breaks the transmission by hydrolysis of the ester.

Zeller and Bissegger (1943) suggested that acetylcholine could unite by a 2-point attachment to cholinesterase. One union occurs at the positively charged quaternary nitrogen atom to a negative site in the enzyme. The other union is effected between the ester group of acetylcholine and another active enzyme site. This union appears to be an essential mechanism in the hydrolytic process of acetylcholine into choline and acetic acid.

Nachmansohn (1959) presented further evidence to show that the active surface of cholinesterase is formed by two functionally and spatially separated esteratic subsites. One of these sites is the receptor at which a nucleophilic group forms a covalent bond with the carbon atom of the carbonyl group of the acetylcholine molecule. The other is an anionic site, which attracts the cationic group in the acetylcholine molecule by coulombic and van der Waals' forces. This combination orients the substrate on the protein surface and enhances enzymic activity. In the first phase of hydrolysis, an acetyl enzyme and choline are formed. In the second phase, the acetyl enzyme reacts with water to form acetate and the restored enzyme. The tetrahedral structure of the quaternary group in acetylcholine suggests the folding of the protein around the spherically shaped molecule.

Choline, acetylcholine, and pilocarpine are all parasympathomimetic drugs. Their action is upon the effector cells in the viscus innervated by the cholinergic fibers. These substances act upon the effector cells directly. Physostigmine and neostigmine emulate the action of these parasympathomimetic drugs, but they do so by combining with the cholinesterase in the target cells and preventing the hydrolysis of acetylcholine. Thus they prolong the period of activity of the innervated organ and delay the onset of the refractory period.

The cholinesterase content of the blood serum of an individual is quite constant. The esterase concentration is especially high in the synapses of nerves. The esterase is also present in larger concentrations at neuromuscular junctions, both of cholinergic fibers and their innervated viscera and at the neuromuscular junctions of somatic nerves and striated muscles.

Many chemical compounds serve to inactivate cholinesterase in high dilutions and thus provide a greater intensity of action of acetylcholine. Outstanding among these substances is *diisopropyl fluorophosphate* (DFP). More will be said about these substances in the discussion of cholinesterase inactivators (see pages 586, 592).

### Synthesis of acetylcholine.

Cholinesterase is concerned with the hydrolysis of acetylcholine. The acetylation of choline in tissues has been extensively studied. With the energy available from the adenosine triphosphate (ATP), coenzyme A, and a specific enzyme, *choline acetylase,* choline is readily acetylated in many different tissues. The synthesis may occur in any part of a neuron, but the reaction occurs to the greatest extent in those portions of the neuron where masses of cell bodies are present. For example, finely divided cholinergic nerves lose their capacity to accomplish the synthesis of acetylcholine, but finely divided brain tissue retains this activity. Indeed, an acetone powder preparation of brain retains this power of synthesis.

### Response to epinephrine and norepinephrine.

When the postsynaptic fiber of an adrenergic nerve is stimulated directly or through the liberation of acetylcholine at the synapse, *hormones* are released in the effector cells of the innervated organ. These hormones are epinephrine and norepinephrine. These hormones are stored within the chromaffin granules of the adrenal medulla along with ATP. The granules are the site of the

synthesis of norepinephrine from dopamine (dehydroxyphenylethylamine). The methylation of norepinephrine to epinephrine occurs in the cytoplasm. The adrenal medulla is not the only locus of synthesis of these hormones. There is a similar distribution of norepinephrine, ATP, and *l*-dopa carboxylase in sympathetic nerve fibers. (von Euler, 1958). Indeed, it has been demonstrated that the canine heart is capable of synthesizing norepinephrine from dopamine (Chidsey *et al.*, 1963).

The action of epinephrine and norepinephrine occurs in the effector cells and thus resembles the site of action of acetylcholine. After the postsynaptic adrenergic fibers to an organ have been severed and allowed to degenerate, the sensitization of the structure to the hormones is increased. Cannon and Rosenblueth proposed that the sensitization is due to better contact of the epinephrine with the effector cells. Further, the permeability of the cells of the effector organ may be increased, and the rate of destruction by tissue enzymes may be diminished. It is likely that many factors are involved in this sensitization, and, more work is necessary to understand completely its significance. It is clear, however, that the site of action of the hormones is on the cells of the innervated organ.

Epinephrine is inactivated in the tissues by the enzymes ortho-methyltransferase and amine oxidase. It has been suggested that drugs which mimic the action of epinephrine, namely, the *sympathomimetic amines,* exert their sympathetic response by competing with epinephrine for these tissue enzymes. Thus the enzymes are inactivated at the expense of the sympathomimetic amine's delaying the destruction of epinephrine by these enzymes.

There are available many agents which will block the actions of the adrenergic hormones at the effector cells. The alkaloid from ergot, *ergotamine,* and *tolazoline* (*Priscoline*), a synthetic compound, are examples. It is believed that there are two receptor sites available to the adrenergic hormones in the receptor cells. One of these is concerned with the excitatory response of these agents, *alpha receptors,* and the other is involved in their inhibitory activity (Ahlquist, 1948). Lands (1952) is of the opinion that the *m*-hydroxyl group in the molecule is the point of union with the excitatory receptors. On the other hand, the hydroxyl group in the aliphatic side chain is the site of union with the *beta* or *inhibitory receptors.* Lands holds the view that the sympathetic receptor in the heart is one of an undifferentiated character and hence is stimulated by sympathomimetic amines having an affinity for either alpha or beta receptors.

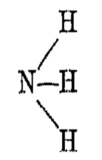
The classical concept of the 2 receptor sites has been extended as other actions of the adrenergic hormones at a cellular level have been delineated. Ahlquist and Levy (1959) proposed the following extension of his hypothesis: *alpha* receptors for contraction of smooth muscle; *beta* receptors for the relaxation of smooth muscle other than the intestine, and also for increases in rate and force of cardiac contraction; *gamma* receptors concerned with glycogenolysis; and *delta* receptors for the inhibition of intestinal smooth muscle (Furchgott, 1959). Mayer and Moran (1960) produced evidence to indicate that the adrenergic receptors for glycogenolysis in the heart are of the *beta* type. The question remains unanswered as to whether or not the stimulation of the myocardium by the adrenergic hormones is sequential to the direct stimulation of the phosphorylase system. Thus the problem of whether there are 3 or 4 receptor sites will await further investigation.

The typical adrenergic blocking agents have a strong affinity for the alpha receptors. Here it is probable that they enter into competition with epinephrine and norepinephrine for the receptor sites and block the excitatory activity of the hormones. Other chemical structures thwart the action of the adrenergic hormones not by virtue of blockade at the receptor sites, but by interfering with the release and/or distribution of the neuronal transmitters at the adrenergic neuromuscular junction. Guanethidine (see page 688), used in the treatment of hypertension, is a compound of this type.

### Acetylcholine and epinephrine.

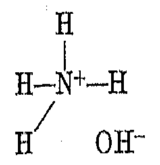
The foregoing discussion has endeavored to establish the roles played by acetylcholine, epinephrine, and norepinephrine, respectively, in the autonomic nervous system. It is of interest to consider these important hormones from the point of view of their chemical constitutions. This is of special interest because in the body the adrenal medulla can serve as a source of each substance.

Each hormone may be considered as an ammonia derivative. Choline is an ammonia derivative. It may be considered as a possible source of epinephrine. The accompanying formulas are of interest. The quaternary ammonium structure of choline is shown.



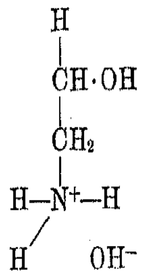
$$\begin{array}{c}\mathrm{H}\\ \mathrm{N{-}H}\\ \mathrm{H}\end{array}$$

Ammonia



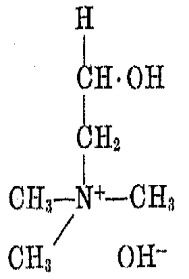
$$\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{H{-}N^+{-}H}\\ \mathrm{H}\quad\mathrm{OH^-}\end{array}$$

Ammonium Hydroxide



$$\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{CH{\cdot}OH}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{H{-}N^+{-}H}\\ \mathrm{H}\quad\mathrm{OH^-}\end{array}$$

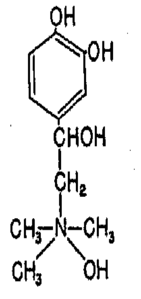
Ethanol Amine
(Hydroxide Form)



$$\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{CH{\cdot}OH}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_3{-}N^+{-}CH_3}\\ \mathrm{CH_3}\quad\mathrm{OH^-}\end{array}$$

Trimethyl Ethanol
Ammonium Hydroxide
Choline

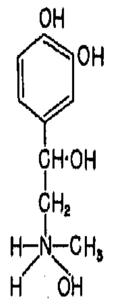
If one replaces the hydrogen atom of the ethanol group in choline with a catechol nucleus, N-dimethyl epinephrine hydroxide is formed accordingly (see formula).



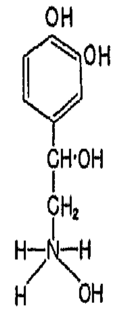
N-dimethylepinephrine

Choline is parasympathomimetic; on the blood pressure it is a depressor. By the introduction of the aromatic nucleus into the molecule the compound becomes a sympathomimetic substance. It is a pressor substance but much weaker than epinephrine. If one progressively demethylates the foregoing compound the pressor response is enhanced. The monomethyl compound is epinephrine, and the compound devoid of methyl groups is *arterenol*, or *norepinephrine*, which is about 2 times more active than the hormone epinephrine as a pressor.

The relationship of epinephrine to norepinephrine is shown in the accompanying formulas.



Epinephrine
(Hydroxide Form)



Norepinephrine
Arterenol
(Hydroxide Form)

The actions of these compounds on the blood pressure of the cat were studied quantitatively by Stehle *et al.* (1936). The response is shown in figure 33-3.

These data show the interesting relationship existing between the structure of choline and epinephrine and how modifications of these structures affect the character of the autonomic action of the compounds. In figure 33-3 the pressor response evoked by 0.01 mg. of norepinephrine is of the same order of magnitude as that produced by 5 mg. of N-dimethylepinephrine (N-trimethyl norepinephrine), showing the pressor potency ratio between the two compounds of 1:500.

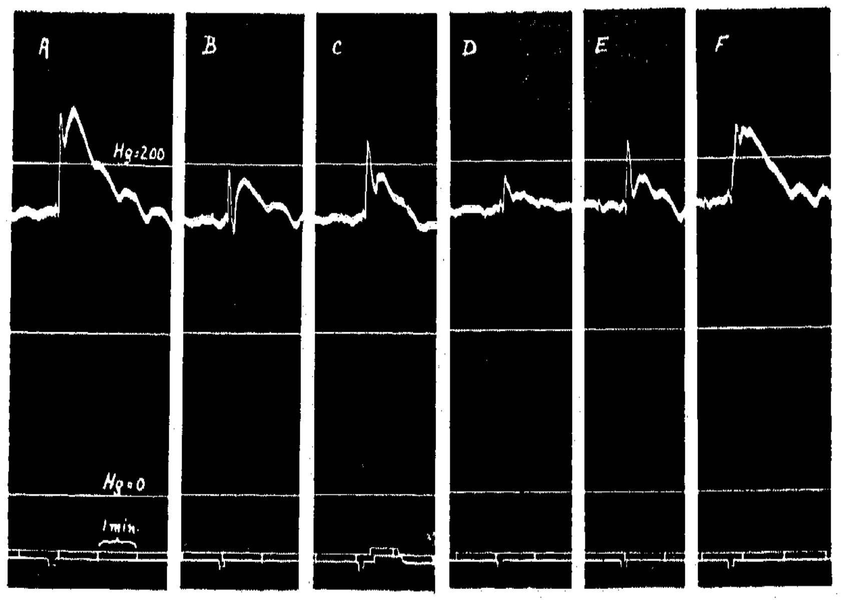


FIG. 33-3. Action of norepinephrine and methylated derivatives on the blood pressure in the cat under Amytal anesthesia. *A*, 0.01 mg. norepinephrine; *B*, 0.01 mg. epinephrine; *C*, 0.1 mg. N-methylepinephrine; *D*, 1.0 mg. N-dimethylepinephrine; *E*, same as *C*; *F*, same as *D* but 5 mg. (From R. L. Stehle, K. J. Melville, and F. Oldham, J. Pharmacol. & Exper. Therap., **56**: 473, 1936.)

TABLE 33-1
*Principal Autonomic Drugs*

| Autonomic Ganglia | Parasympathetics | Sympathetics |
|---|---|---|
| **Stimulants**<br>Acetylcholine<br>Physostigmine<br>Neostigmine<br>Pyridostigmine (Mestinon)<br>Nicotine (small doses) | **Cholinergic agents**<br>Acetylcholine<br>Beta-methylacetylcholine chloride (Mecholyl)<br>Carbaminoylcholine<br>Urecholine<br>Choline<br>Muscarine<br>Pilocarpine<br>Physostigmine<br>Neostigmine<br>Pyridostigmine (Mestinon)<br>Tensilon<br>Mytelase<br>Arecoline<br>DFP | **Adrenergic agents**<br>Epinephrine<br>Arterenol<br>Ephedrine<br>Amphetamine<br>Synephrine<br>Neosynephrine, phenylephrine, and other sympathomimetic amines |
| **Blocking agents**<br>Nicotine (large doses)<br>Acetylcholine (large doses)<br>Tetraethylammonium chloride<br>Hexamethonium chloride<br>Ansolysen<br>Mecamylamine (Inversine)<br>Ecolid | **Cholinergic blocking agents**<br>Atropine<br>Hyoscine<br>Hyoscyamine<br>Homatropine, and synthetic atropine-like compounds | **Adrenergic blocking agents**<br>Ergotoxine<br>Ergotamine<br>Dihydroergotamine<br>Dibenzyl-β-chlorethylamine<br>Dibenzyline<br>Certain dioxane derivatives<br>Phentolamine (Regitine)<br>Tolazoline (Priscoline)<br>Ilidar |

## Principal autonomic drugs.

Table 33-1 shows the principal autonomic drugs, the type of response elicited, and the division of the autonomic nervous system which responds to their action.

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# 34

# *Sympathetic Division of the Autonomic Nervous System (Sympathomimetic Agents)*

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## EPINEPHRINE (ADRENALIN)

Epinephrine and norepinephrine are the hormones of the sympathetic division of the autonomic nervous system. Epinephrine has been used as a medicament for more than a half century. The introduction of norepinephrine into clinical medicine occurred within recent years. In addition to these two hormones there is a large number of substances similar to them in chemical constitution which in the main mimic the action of epinephrine and/or norepinephrine on the effector cells of the sympathetic nervous system.

These substances, collectively, are referred to as the *sympathomimetic amines.* In many respects their application in clinical medicine exceeds that of the hormone epinephrine. To this class of substances belong the alkaloids ephedrine and phenylephrine.

### History of epinephrine.

The following account of the early observations on epinephrine was given by Sir Henry Dale in the Sharpey Schafer Memorial Lecture.

> "In March 1894 I was still a boy, in my last year at school, so that the story, as I know it, came to me some seven years later from those who, like the late Sir William Bayliss and the late Professor Benjamin Moore, were in the laboratory at University College, London, at the time. And the story, as it thus came to me, was remarkable enough. Dr. Oliver, I was told, was a physician in practice, who had a liking and a "flair" for the invention of simple appliances, with which observations and experiments could be made on the human subject. Dr. Oliver had invented a small instrument with which he claimed to be able to measure, through the unbroken skin, the diameter of a living artery, such as the radial artery at the wrist. He appears to have used his family in his experiments, and a young son was the subject of a series, in which Dr. Oliver measured the diameter of the radial artery, and observed the effect upon it of injecting extracts of various animal glands under the skin. One feels that the name of the young Oliver might well be handed down, in physiological history, with that of Dr. William Beaumont's celebrated patient, Alexis St. Martin. We may picture, then, Professor Schafer, in the old physiological laboratory at University College, London—a dingy haunt it would appear to those accustomed to our modern standards—finishing an experiment of some kind, in which he was recording the arterial blood pressure of an anaesthetised dog. I can find no contemporary record even to suggest what the experiment might have been. To him enters Dr. Oliver with the story of the experiments on his boy, and, in particular, with the statement that injection under the skin of a glycerin extract from calf's suprarenal gland was followed by a definite narrowing of the radial artery. Professor Schafer is said to have been entirely sceptical, and to have attributed the observation to self-delusion—an attitude on the part of the experimental expert which our clinical colleagues may have encountered. He can hardly be blamed, I think; knowing even what we now know about the action of this extract, which of us would be prepared to believe that injecting it under a boy's skin would cause his radial artery to become measurably more slender? Dr. Oliver, however, is persistent; he indicates that the Professor has a dog prepared for recording vascular effects, and suggests that, at least, it will do no harm to inject into its circulation, through a vein, a little of the suprarenal extract, which he produces from his pocket. So Professor Schafer makes the injection, expecting a triumphant demonstration of nothing, and finds himself standing 'like some watcher of the skies, when a new planet swims into his ken,' watching the mercury rise in the manometer with amazing rapidity and to an astounding height, until he wonders whether the float will be thrust right out of the peripheral limb. So the discovery was made of the extraordinary active principle in the suprarenal gland, later found to come only from the medulla of the gland, and still later obtained as a pure, crystalline substance, and variously named epinephrine or adrenalin."

**The isolation of epinephrine.** Epinephrine was the first hormone to be isolated and also the first to be synthesized. The importance of the adrenal glands in physiology was recognized by Brown-Séquard and d'Arsonval. In 1891 the former wrote, "These internal secretions whether by direct favorable influence or through the obstacles they oppose to deleterious processes, seem to be of great utility in maintaining the organism in its normal state." The pressor principle of the glands was demonstrated by Oliver and Schaefer (1895). This pharmacologic activity of the extracts of the adrenal glands aroused the interests of biochemists and pharmacologists. The pioneer investigators in this field were von Fürth in Germany and Abel in America.

Abel and Crawford (1897) separated the hormone epinephrine from the medullary portion of the adrenal gland in the form of its polybenzoyl derivative. By decomposing the benzoyl derivative with hot dilute sulfuric acid, they obtained a very active pressor substance. Abel (1899) found that the compound was represented by the empirical formula, $C_{17}H_{15}NO_4$.

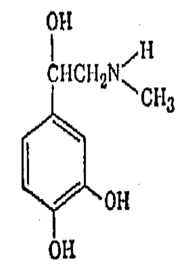
In the autumn of 1900 the Japanese chemist Takamine* visited Abel's laboratory and showed interest in Abel's procedure of isolation. He stated that "no doubt it could be improved and simplified." Returning to his laboratory, Takamine treated the purified extract of the glands obtained by Abel through benzoylation with ammonium hydroxide. Epinephrine separated in burr-like crystals (Takamine, 1901). Takamine named the product adrenalin. Takamine's product was not entirely pure. It remained for Aldrich (1905) to obtain crystals and assign the true empirical formula $C_9H_{13}NO_3$. If one subtracts a benzoyl group ($C_6H_5CO$) from the formula assigned by Abel, one obtains $C_{10}H_{10}NO_3$ which is close to the actual formula of the hormone.

Takamine and von Fürth and others soon conducted experiments to elucidate the structure of epinephrine. Stolz (1904) synthesized epinephrine and norepinephrine upon the assumption that the structural formula assigned to epinephrine was correct.

### Epinephrine, U.S.P.

Epinephrine occurs as a white or light brownish, microcrystalline, odorless powder. It darkens upon exposure to air. It is very slightly soluble in water but dissolves readily in water acidified with hydrochloric acid. The acid unites with the epinephrine base, forming the soluble hydrochloride. The United States Pharmacopeia recognizes only the *levo*-epinephrine, which is the naturally-occurring hormone. When the compound is synthesized, the racemic form is obtained. When resolved into its *d*- and *l*-isomers one finds that the *d*-epinephrine is about $1/20$ as active as the *l*-epinephrine. The racemic variety is therefore about $1/2$ as active as the *l*-compound. Owing to the difficulties involved in resolving the racemic variety into its optically active isomers, most of the epinephrine used in medicine today is natural epinephrine.

The structure of epinephrine is shown in the formula below:



Epinephrine
Adrenalin
(3,4-dihydroxy-α-[methylamino methyl]—benzyl alcohol

In 1944 it was discovered that extracts of the suprarenal glands contain norepinephrine as well as epinephrine. In 1948 James showed that the two hormones could be separated by chromatography. A convenient method for the relative estimation of the two hormones in suprarenal extracts was developed by von Euler and Hamberg (1949). Von Euler and his associates (1950) isolated norepinephrine from suprarenal gland extracts by the counter current distribution technic. Goldenberg *et al.* introduced norepinephrine as a therapeutic agent in 1949. Crystalline epinephrine, including the U.S.P. Reference Standard epinephrine samples, contained from 10.5 to 18.5 per cent of norepinephrine. It is unusual indeed that this comparatively high percentage of norepinephrine, present presumably in all natural epinephrine used, should have remained undetected for a half century. Epinephrine is available at present almost completely (less than 0.1 per cent) devoid of norepinephrine.

The most generally used preparation of epinephrine is the 1:1000 injection of the hydrochloride of the base. This solution is usually preserved from bacterial contamination by the addition of a small amount (0.5 per cent) of chlorobutanol. Upon exposure to air, epinephrine hydrochloride solutions (especially if dilute) gradually undergo oxidation. The solutions acquire a pink, red, and finally a brown color. To protect against oxidation through atmospheric influence, small quantities of sodium acid sulfite (0.1 per cent) are added.

The oxidation of epinephrine by oxidizing agents or by catechol oxidase has been studied by Richter and Blaschko (1937). They oxidized epinephrine with potassium iodate in acetic acid solution and obtained a definite chemical compound with a red pigment referred to as *iodoadrenochrome.* The oxidation of epinephrine proceeds according to the following formulas, page 540. Adrenochrome is quite unstable and in alkaline solutions undergoes decomposition, forming melanin pigments.

### Origin of epinephrine in the adrenal medulla.

The origin of epinephrine in the adrenal medulla has been the focus of many biochemical investigations. It appears to be agreed that epinephrine is formed from tyrosine as follows:

1. The introduction of a second hydroxyl group on the ring in the tyrosine molecule (dihydroxyphenylalanine, "dopa")

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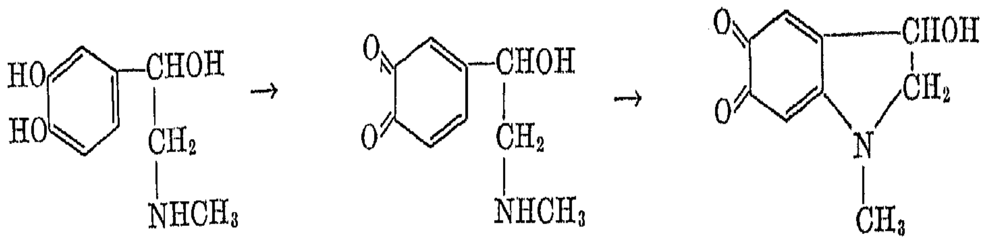
* Later Takamine was deputized by the government of Japan to arrange for the planting of the cherry trees in Washington as a token of good will between the two nations.



Epinephrine — $o$-Quinone Derivative — Adrenochrome

2. Decarboxylation (dopamine)
3. Introduction of the side chain hydroxyl group (norepinephrine)
4. N-methylation (epinephrine)

The proposed synthesis of the hormone is of special interest because it shows norepinephrine to be the immediate precursor of epinephrine. Bülbring (1949) showed that suspensions of minced suprarenal glands from either the dog or cat are capable of methylating norepinephrine and thus forming epinephrine. Further evidence was produced by Kirshner and Goodall (1957), who showed that norepinephrine was methylated with S-labeled adenosylmethionine in the supernatant liquid from adrenal medulla homogenates. The norepinephrine content of the suprarenal glands of different species varies greatly; that of the rabbit is low (0.02 mg./gm. or less, while that of the whale averages 1.5 mg./gm. (von Euler, 1954).

Epinephrine and norepinephrine (catecholamines) are synthesized by other tissues. They may be produced in sympathetic nerve endings, and the heart has been shown to synthesize the catecholamines (see page 666). Axelrod (1963) demonstrated the presence of an enzyme in the microsomes of rabbit liver that was capable of synthesizing epinephrine. The activity of the enzyme is dependent upon the reduced form of nicotinamide adenine dinucleotide phosphate. The enzyme appears to be nonspecific and can produce the catecholamines from such substances as phenol and estradiol. The main pathway of synthesis is shown in the preceding paragraph.

The normal epinephrine level of peripheral venous human plasma appears to be less than 0.1 μg./L. and that of norepinephrine, less than 0.5 μg./L. These values are markedly augmented during insulin hypoglycemia and in patients with pheochromocytoma.

### Pharmacologic responses to epinephrine.

**Effect on the blood pressure.** The dramatic effect which arises from the intravenous injection of a solution of epinephrine is the prompt rise in blood pressure. When 0.2 ml. of a solution of 1:10,000 of epinephrine is injected intravenously into a dog, the blood pressure promptly rises. This is the result of peripheral vasoconstriction, myocardial stimulation, and an increase in heart rate. During the peak period of pressor response a bradycardia may occur as a result of compensatory vagal activity evoked by the carotid sinus and aorta reflexes. The vagal effects may be blocked by the previous administration of atropine. The blood pressure rapidly falls to the normal level and then slightly below normal. The final depressor response is due to vasodilatation which only becomes manifest after the preponderating, fleeting action on the arterioles has disappeared.

Little tolerance is developed to the pressor response of epinephrine by the repeated injection of small doses. However, large doses injected repetitiously show a diminished pressor response.

The degree of arteriolar constriction evoked by the drug is different in various structures. The maximal constriction occurs in the splanchnic area; the kidney arterioles are strongly constricted. Constriction is also marked in the skin and mucous membranes. The arterioles in skeletal muscle are dilated by epinephrine. In this respect epinephrine differs from norepinephrine. With norepinephrine the dilator component is absent except on the coronary vessels. Intra-arterial infusions of epinephrine in the leg of man produce vasodilatation. Those made with norepinephrine cause vasoconstriction. The action of very diluted solutions of epinephrine, especially when studied by perfusion methods, is predominantly dilating.

The coronary arteries in man are not markedly affected by epinephrine. Although it is claimed that epinephrine will actually dilate the coronary arteries in man, the evidence is not clearly convincing. Katz and Lindner (1939) found that epinephrine dilated the coronary arteries of the arrested heart of the dog. However, this dilatation was preceded by a period of constriction. Berne (1958) showed that intracoronary injections of epinephrine and norepinephrine in the beating, fibrillating, or arrested dog heart produced an initial period of decreased coronary blood flow of short duration. This was followed by a period of longer duration in which the coronary blood flow was increased, with a concomitant reduction in coronary sinus blood-oxygen tension. The myocardial oxygen consumption was increased to a greater degree than was the coronary flow of blood. These results are interpreted to indicate that the primary effect of the catecholamines upon coronary vessels is that of constriction, and that the secondary effect of vasodilatation with increased coronary blood flow is sequential to the increased demand for oxygen by the myocardium evoked by the drugs. In addition, the dilatation may possess a passive component because of the strong arteriolar constriction elsewhere in the body. Dunn *et al.* (1961), in their measurements of myocardial blood flow in dogs rendered hypovolemic by hemorrhage, observed that norepinephrine evoked a greater increase in blood flow than did epinephrine, phenylephrine, or metaraminol.

Persons with angiospastic disease are frequently brought into an acute attack by the injection of epinephrine. It appears that if coronary dilatation does occur, it is insufficient to oxygenate the heart to compensate for the additional work imposed upon the heart by the action of the drug. In angina pectoris there is often a downward displacement of the S-T segment of the electrocardiogram. Epinephrine injections likewise may produce this electrocardiographic change. It is a safe policy to avoid the use of epinephrine in individuals with angiospastic disease.

Greever and Watts (1959) studied the peripheral arterial blood levels in dogs in the various stages of irreversible hemorrhagic shock. The epinephrine concentration in the arterial blood increased from control levels of less than 1 μg./L. to a maximum of 29 μg./L. when the arterial blood pressure was held at 40 mm. Hg. They suggest that the increased levels of circulating epinephrine are sufficient to account for the intense vasoconstriction of early shock. Poole and Watts (1959) demonstrated that the arterial blood level of epinephrine was far greater than the venous level. These differences were measured in the femoral artery and femoral vein, and these authors state that the arteriovenous epinephrine level differences represent the inactivation of epinephrine in skeletal muscle.

In similar experiments in rabbits Coleman and Glaviano (1963) showed that during shock the catecholamine content of the heart and brain dropped significantly. Increases were observed in the spleen, whereas the liver and skeletal muscle levels remained unchanged. It is difficult to assess these changes as altered catecholamine production or rates of utilization. Perhaps these changes in catecholamine levels in various organs during shock reflect altered blood transport as well as changes in rates of synthesis and degradation.

Kosakaé (1927) showed that epinephrine solutions caused constriction of the placental blood vessels. These are without nerve supply. The experiment is of importance, because it shows the constricting activity of epinephrine directly on a vascular structure without the presence of adrenergic nerves.

**Action on the heart.** Epinephrine stimulates the effector cells of the cardiac accelerator nerve but simultaneously reflexly stimulates the vagus through the carotico-aortic pressoreceptor mechanisms. The vagal effect predominates, and the heart rate is slowed. The beats are strong and forceful. Frequently the myocardium escapes from vagal inhibition, and the full accelerating effect of epinephrine becomes manifest. After atropine the vagal effect of epinephrine is abolished. In atropinized animals, epinephrine produces a more efficient atrial and ventricular beat, as well as accleration of rate.

In perfusion experiments in cold-blooded animals, epinephrine can be readily demonstrated to evoke a direct stimulating action on the myocardium. A heart which has come to a standstill can often be made to beat again by the direct application of a solution of epinephrine, 1:100,000. The direct stimulating effect of epinephrine continues for some time. The oxygen consumption of the heart is increased as a result of increased rate and force of beat. Epinephrine as such did not increase the oxygen uptake of slices of the cat's heart when studied by the Warburg technic. Ouabain and other cardiac glycosides, however, elicited increased cardiac respiration under the same conditions (Herrmann *et al.*, 1954).

Evidence emanating from different sources indicates that the positive inotropic action of the catecholamines is associated with an increase in phosphorylase activity evoked in the tissue by these hormones. The phosphorylase activity is dependent upon the formation of 3′,5′ cyclic adenosine monophosphate from adenosine triphosphate. Dinitrophenol, which inhibits energy-rich phosphate bond transfers, blocks the inotropic action of the catecholamines on the heart (Ellis, 1952). Belford and Feinleib (1962) demonstrated that the inotropic effect of the catecholamines on the heart was concomitant with an increase of the glucose-6-phosphate level. It appears that glucose-6-phosphate levels increase with phosphorylase activity (Ellis *et al.*, 1957). The potency of inotropic effect of the catecholamines appears to parallel the glucose-6-phosphate level and, similarly, the phosphorylase activity of the tissue.

Other agents evoking an inotropic action on the heart, such as aminophylline and calcium salts, increase the glucose-6-phosphate level and phosphorylase activity. These observations, originating with the work of Sutherland and Rall (1958) related to the phosphorylase activity of the catecholamines on the liver, appear to have broad implications.

The direct action of epinephrine on the myocardium may also be harmful. In sufficient concentrations the drug may produce cardiac dilatation and ventricular fibrillation. The beneficial effects obtained are produced by an optimal concentration of the hormone, which must be determined in each case from the resulting pharmacologic syndrome. The direct cardiac-stimulating action of epinephrine has clinical application when the heart of a normally healthy individual comes to acute arrest. This may occur in drowning, hypoxia of the newborn, and in anesthetic accidents. Time is a most important factor; the drug must be injected intravenously at the first signs of threatened cardiac arrest. The solution is promptly injected into the jugular vein; 0.05 to 0.1 ml. of the 1:1000 solution, previously diluted to about 5 ml. with normal salt solution, is generally employed. If the heart has stopped beating, no advantage is gained by intravenous injection. The drug is then administered by intracardiac injection. From 0.5 to 1 ml. of the 1:1000 solution is injected directly into the right atrium. A long, narrow-gauge hypodermic needle is forced through the 4th intercostal space just adjacent to the sternum. Cardiac massage and artificial respiration should also be instituted.

In long experience with this method of combating cardiac arrest with various laboratory animals, especially the dog, our observation has been that success is dependent upon promptness of injection. After 10 minutes revival seldom takes place. This observation has been confirmed in man by various investigators.

**Release of catecholamines.** It has been well established by Burn and Rand (1958) that reserpine depletes the catecholamine stores of the vascular walls. This sensitizes the vessels to catecholamine action in a similar manner to denervation. However, this abolishes the response to noncatechol pressor agents such as tyramine. It is likely that the action of these agents is mediated through the liberation of norepinephrine and that after depletion they fail to evoke a response. Cocaine appears to intensify the response of pressor catecholamines by preventing the release of norepinephrine from the cells, and provokes a sensitization similar to the foregoing depletion mechanism. Weiner *et al.* (1962) postulated that nicotine liberates catecholamines from nerve terminals and from chromaffin granules of the adrenal medulla and from those associated with sympathetic nerve fibers. Tyramine depletes a third compartment, in which circulating catecholamines are bound. This third compartment is the locus of uptake of exogenous catecholamines.

**Local effect upon the blood vessels.** The local application of epinephrine solution to mucous membranes causes prompt vasoconstriction. If injected subcutaneously, the same effect is elicited. When solutions as dilute as 1:100,000 are employed, this localized vasoconstriction is produced with scarcely any effect upon the systemic blood pressure.

The spraying of a 1:10,000 to 1:1,000 solution of epinephrine on the membranes of the nose or throat during surgical procedures will check hemorrhage and produce an ischemia in the area. Epistaxis is readily checked by the insertion of a pledget of cotton containing 1:1000 epinephrine solution into the nasal cavity.

The ischemic effects of the drug are used to localize the action of local anesthetics of the procaine type which do not themselves produce vasoconstriction. For this purpose a concentration of 1:100,000 is used, dissolved directly in the 2 per cent procaine hydrochloride solution.

**Effect on the respiration.** Upon intravenous injection, epinephrine evokes a transient and variable effect upon the respiration. It lasts approximately as long as the blood pressure effect. At the peak of the pressor response, the respiration may temporarily be increased in rate and amplitude. This is followed intermittently by apnea or very shallow and slow respiration. The respiration effect of epinephrine is sequential to its pressor action and results from carotid chemoreceptor stimulation. Adrenergic blocking agents such as Dibenamine will reverse the pressor response to epinephrine, but the transitory apneic effect on the respiration is not altered.

**Effect on bronchial muscle.** Perhaps the most prevalent clinical use of epinephrine is in the treatment of asthma. The bronchioles are innervated by adrenergic fibers which are relaxant in effect. When the effector cells are stimulated by the injection of epinephrine, the bronchioles relax. The action is more marked if the musculature has been previously contracted by the use of histamine or a cholinergic drug like pilocarpine. The value of epinephrine in the treatment of asthma lies in its promptness of action and its reliability.

In figure 34-1 the action of epinephrine and pilocarpine on the bronchiolar musculature may be observed. Simultaneously the blood pressure effects are recorded. The data set forth in the tracing emphasize that on the bronchiolar muscles contraction is produced by stimulating the effector cells of the cholinergic nerves (pilocarpine). Bronchial dilatation is produced by stimulation of the effector cells of the adrenergic nerves (epinephrine).

Frequently in the treatment of asthma epinephrine and the sympathomimetic amines are used in the form of aerosols. Dautrebande and Heymans (1961) demonstrated on the excised, perfused lungs of guinea pigs the efficacy of this method of administration. With as little as 1 to 2 breaths with an aerosol of isoproterenol, maximal dilatation results. They estimated that with each breath the number of microparticles of the dilator aerosol penetrating into the lungs was 2 million/ml. of air.

The problem of epinephrine fastness occasionally encountered in patients may be due to the

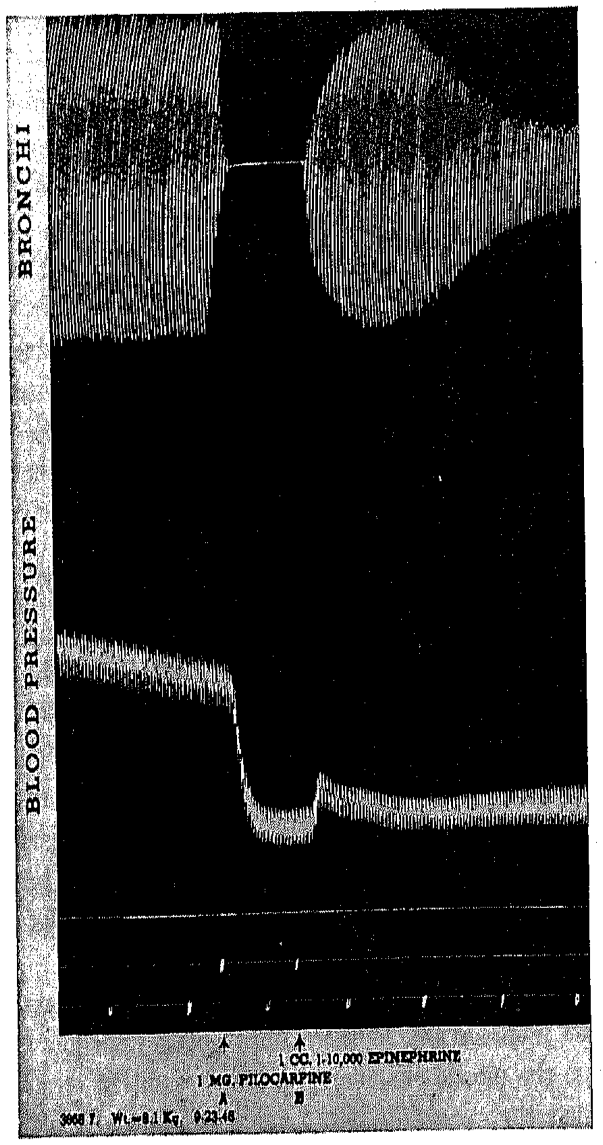


Fig. 34-1. The action of epinephrine and pilocarpine on the bronchioles. (From *Research Today*, Eli Lilly and Company, 1947.)

release of histamine from the tissues of the host. It is sometimes obliterated by the administration of one of the antihistaminics. The investigations of Blumenthal *et al.* (1956) have elucidated this problem. It appears to have been established by various animal experiments that the pharmacologic responses to epinephrine are diminished by lowering the pH of the medium. On the other hand, the action of acetylcholine is enhanced by lowering, and decreased by increasing the pH. Blumenthal *et al.* studied the pharmacologic response to epinephrine in human volunteers upon intravenous injection. Changes in blood pH were achieved by carbon dioxide inhalation and hyperventilation, respectively. With the blood pH at 7.22, 0.3 ml. of epinephrine, 1:20,000, produced no appreciable acceleration of the heart rate; at pH 7.60 the same dosage level nearly doubled the heart rate. These investigators are of the opinion that epinephrine fastness is due at least in a great part to either general or local acidosis. They recommend 120 to 150 ml. of molar sodium lactate intravenously to combat the acidosis and thus counteract the epinephrine fastness by facilitating the action of epinephrine and diminishing the response to acetylcholine.

Wood *et al.* (1963) contributed further evidence of the effect of acidosis on the response to epinephrine. They demonstrated in dogs that hypoxia and acidosis can strikingly reduce the amplitudes of the pressor and depressor responses to epinephrine. The depressor component was more readily obliterated by respiratory acidosis than was the pressor component.

**Action on the uterus.** The effect of epinephrine on the uterine musculature enjoys a wide species variation. Whether relaxation or contraction occurs depends upon the relative tone of the inhibitory and motor adrenergic fibers. Also, the pregnant uterus may respond to epinephrine differently from the nongravid uterus. For example, in the cat the nongravid uterus is relaxed by epinephrine, but the gravid uterus is contracted by the drug. In the rat and guinea pig the gravid and nongravid uteri are relaxed by epinephrine, but in the rabbit in the pregnant and virgin state, the uterus is contracted by epinephrine.

Isolated strips of nongravid human uteri are generally made to contract more forcibly by the addition of epinephrine to the muscle chamber. Daels (1941) observed that the excised human uterus, whether gravid or nongravid, was affected by epinephrine in the following manner. The exterior, propulsive muscular layer was stimulated, while the interior and cervical layer was inhibited. Each response would facilitate parturition. Garrett (1955) confirmed the stimulating effect of epinephrine on excised human uterine strips. He observed that norepinephrine shares this activity with epinephrine and enjoys a greater stimulating action on the nonpregnant myometrium than does epinephrine

At term, strong uterine spasticity *in situ* is overcome by epinephrine. The force of uterine contractions is diminished, and hourglass uterine contraction is often relaxed. For this purpose 0.3 to 0.5 ml. of epinephrine solution, 1:1000, is used subcutaneously.

Woodbury and Abreu (1944) studied the effect of epinephrine on the human gravid uterus at term. They inserted a balloon into the uteri of women 9 months pregnant. This balloon was filled with a sterile sulfanilamide solution, and the apparatus to measure the uterine contractions was attached. Epinephrine solutions 0.01 to 0.1 mg. were injected intravenously (rapid administration), and 0.01 to 0.02 mg., well diluted, were given by slow injection. The latter dosage was to simulate the clinical subcutaneous or intramuscular injection. They observed that the slow administration of small doses of epinephrine reduced the amplitude of uterine contractions prior to the period of uterine inhibition. Each effect was pronounced. These investigators suggest that "epinephrine may reduce Bandl's ring and contraction rings if they occur."

It appears from these studies that the action of epinephrine upon the human gravid uterus *in situ* resembles its effect upon the blood vessels, in which the inhibitory effects outlast the excitant action. Furthermore, small doses of epinephrine administered subcutaneously elicit only the inhibitory effect upon the uterus.

It is interesting to note that the work of Rudzik and Miller (1962) suggests that the relaxant action of relaxin on the uterus is due to the release of catecholamines. The catecholamines have been identified in the amniotic fluid; they are presumed to be of maternal origin (Koren *et al.*, 1961).

**Action on the gastrointestinal tract.** An intravenous injection of epinephrine causes a prompt cessation of movements of the stomach and intestines. Simultaneously the mesenteric vessels are constricted, and the mesentery appears blanched. This is readily observed in a laparotomized rabbit with the gastrointestinal tract partially exteriorized. The splanchnic nerves are relaxant to the wall of the intestine and constrictor to the pyloric, ileocolic, and internal anal sphincters. Therefore the over-all action of epinephrine on the gastrointestinal tract is constipative in character. It retards the propulsion of the food bolus.

Gruber and Matthews (1953) observed that many of the sympathomimetic amines share this property of relaxing the intestine with epinephrine. Isopropyl arterenol (Isuprel) is an exception. Cocaine administered prior to epinephrine or norepinephrine potentiated the intestinal relaxation elicited by each of these compounds.

Goodford and Hermansen (1960) studied the rate of sodium ion exchange in intestinal smooth muscle. The rate was found to be rapid—about 50 times faster than the rate of potassium exchange. Mechanical changes were recorded simultaneously with the loss of $Na^{24}$. As epinephrine was added and caused the muscle to relax, the loss of sodium was about doubled. Sodium uptake was also inhibited in the presence of epinephrine. Bülbring (1960) suggests that the relaxation of intestinal smooth muscle elicited by epinephrine is mediated "by stimulating one reaction in a chain of metabolic cycles which finally supply energy for an electrogenic sodium pump, thereby stabilizing the membrane."

The gall bladder is relaxed by epinephrine, and the bile duct is contracted by epinephrine.

**Action on the urinary bladder.** The local application of diluted solutions of epinephrine to the wall of the bladder produces marked vasoconstriction. The intravenous injection of the drug increases the tone of the trigone and causes the contraction of the internal vesical sphincter. The wall of the bladder is relaxed, and the desire to void is delayed.

Epinephrine causes an actual increase in urine secretion. This is the result of the increase in blood pressure, producing a greater effective glomerular filtration pressure. The renal vessels are at first constricted, and little urine is secreted. They dilate, however, more promptly than do many of the other vessels.

**Effect on the eye.** The superior cervical sympathetic ganglion supplies fibers to the radial muscle of the iris which are adrenergic in character. An intravenous injection of epinephrine causes active pupillary dilatation. Since the dilatation is not mediated through the ciliary nerves, concomitant cycloplegia does not occur, as it does with atropine mydriasis. In addition to mydriasis, the intravenous injection of epinephrine causes exophthalmos and the withdrawing of the nictitating membrane.

The entire ocular syndrome of epinephrine occurs after the cervical sympathetic nerves have been severed. It is actually intensified if the nerves have been permitted to degenerate.

When applied locally to the eye, epinephrine does not produce as marked mydriasis as do other sympathetic stimulants. It does, however, evoke a degree of pupillary dilatation and simultaneously produces an ischemia of the conjunctiva.

**Effect on metabolism.** The injection of epinephrine causes an increase in basal metabolic rate without significant alteration of the respiratory quotient. In the white rat the intraperitoneal injection of 0.2 mg./kg. increases the oxygen consumption about 30 per cent. As the respiratory quotient is not significantly changed, the metabolism of all types of food must be accelerated.

The sympathetic nerves to the liver, when stimulated, produce glycogenolysis. Epinephrine produces this type of stimulation. A hyperglycemia caused by the mobilization of hepatic glycogen as blood glucose is therefore produced. The blood sugar level may exceed the renal threshold of 170 mg. per cent, and a transient glycosuria may result. Epinephrine also stimulates glycogenolysis in skeletal muscle. Lactic acid is formed, which may be converted into glycogen in the liver. Other drugs which stimulate the effector cells of the adrenergic nerves produce hyperglycemia. The effects of these drugs, such as ephedrine, are slight compared to the marked hyperglycemia of epinephrine. Harvey *et al.* (1952) showed that a wide variety of adrenergic blocking agents previously injected into the cat or rabbit will suppress epinephrine-induced hyperglycemia.

The mechanism of the glycogenolytic response of the liver to epinephrine has been the subject of numerous investigations at an enzyme level. The action appears to involve the conversion of phosphorylase kinase into an active state by epinephrine or by other catecholamines. The particulate portion of liver homogenates is essential for the epinephrine response. The hormone forms a heat-stable factor. It has been identified as $3',5'$-cyclic adenosine monophosphate, which activates the phosphorylase reaction in cellular preparations in which epinephrine was ineffective. It appears that epinephrine evokes the formation of 3′,5′-cyclic adenosine monophosphate from adenosine triphosphate. The potency of the various catecholamines in activating this phosphorylase reaction in general parallels their hyperglycemic activity (Rall *et al.*, 1957).

Epinephrine also affects lipid metabolism; the action on lipid metabolism is shared also by norepinephrine. The effect is shown by an increase in the circulating free fatty acids after an intravenous injection of epinephrine of 0.05 µg./kg. The rise in free fatty acids occurs within 2 minutes and persists for about 15 minutes. The lipid effect of epinephrine has been demonstrated in a variety of laboratory animals and man (Havel and Goldfien, 1959).

The catecholamines increase the rate of release of free fatty acids and the concentration of the acids within the tissue. This has been demonstrated *in vitro* and *in vivo*. The primary effect of the catecholamines on tissue fat appears to be hydrolytic cleavage. Hagen and Ball (1961) showed that the mobilization of fat by the catecholamines requires neither glucose nor oxygen. Not all of the fatty acids liberated by the hormones are released; a portion is re-esterified into fat with α-glycerophosphate derived from glucose metabolism. This accounts for the increase in glucose phosphorylation and the increase in glucose uptake by adipose tissue evoked by the catecholamines. Thus a portion of the increased oxygen uptake and glucose utilization elicited by the catecholamines is consumed in the re-esterifying of fat, which was hydrolyzed by their action on adipose tissue.

**Miscellaneous effects of epinephrine.** Epinephrine stimulates the effector cells of the pilomotor nerves and causes the *erection of hairs*. This is also mediated through the adrenergic nerves. The sympathetic fibers to the sweat glands are mainly cholinergic; they are stimulated by pilocarpine and depressed by atropine. An injection of epinephrine does not evoke generalized sweating. However, at the site of injection, especially an intercutaneous injection, evidence of sweating becomes manifest. This action is blocked by such adrenergic blocking agents as dibenamine.

In *urticaria* and *angioneurotic edema* the effect of epinephrine is often dramatic. From 0.5 to 1 ml. of a 1:1000 solution is injected subcutaneously. The itching soon subsides and the wheals gradually disappear.

Epinephrine produces a stimulation of *salivary flow*. The saliva is viscid and rich in organic solutes. It differs markedly from the clear, limpid saliva produced by parasympathetic stimulation. The latter contains very small quantities of organic constituents.

Upon local contact epinephrine causes the shrinking of the nasal turbinates and thus provides a more effective air passage.

**Epinephrine blood pressure reversal.** In an animal that has been injected repeatedly with ergotamine until the effector cells of the sympathetic fibers which are constrictor to the arterioles are paralyzed, epinephrine elicits a depressor response. In such an animal only the constrictor component is paralyzed by ergotamine. The effector cells of the dilator fibers are unaffected. Epinephrine stimulates the effector cells of these fibers and evokes a fall in blood pressure. This epinephrine reversal is specific for the hormone epinephrine and is not shared by the other sympathomimetic amines.

The effect of epinephrine on the blood pressure of the pithed cat before and after ergotamine is shown in figure 34-2.

**Oxidation of epinephrine in the tissues.** Upon intravenous injection epinephrine rapidly disappears from the blood stream. It is fixed in the tissues and inactivated chiefly through the action of the enzyme *o*-methyl transferase to *metanephrine* (Armstrong and McMillan, 1959). Metanephrine is oxidized by amine oxidase to vanillo-mandelic acid.

Axelrod and Laroche (1959) showed that *o*-methylation is the principal pathway of metabolism for epinephrine and norepinephrine. Within 2 minutes after the administration of epinephrine to cats, more than ½ of the compound is converted into metanephrine. Pyrogallol prolongs the action of epinephrine by inhibiting the action of *o*-methyl transferase in methylating epinephrine or norepinephrine. It appears that the enzyme *o*-methyl transferase is the enzyme primarily involved in the inactivation of epinephrine and norepinephrine.

Kirshner *et al.* (1958) injected 6 human subjects intravenously with 2-$C^{14}$-labeled *d,l*-epinephrine and studied the products of excretion in the urine. The radioactivity which appeared in the urine was distributed among these various degradation products as follows: epinephrine, 4 per cent; 3-methyl-*o*-epinephrine, 5 per cent; 3-methyl-*o*-epinephrine conjugate, 42 ± 7 per cent; 3-methoxy-4-hydroxymandelic acid, 27 ± 3 per cent; 3,4-dihydroxymandelic acid, 12 ± 4 per cent; and 2 unidentified fractions, 4 per cent.

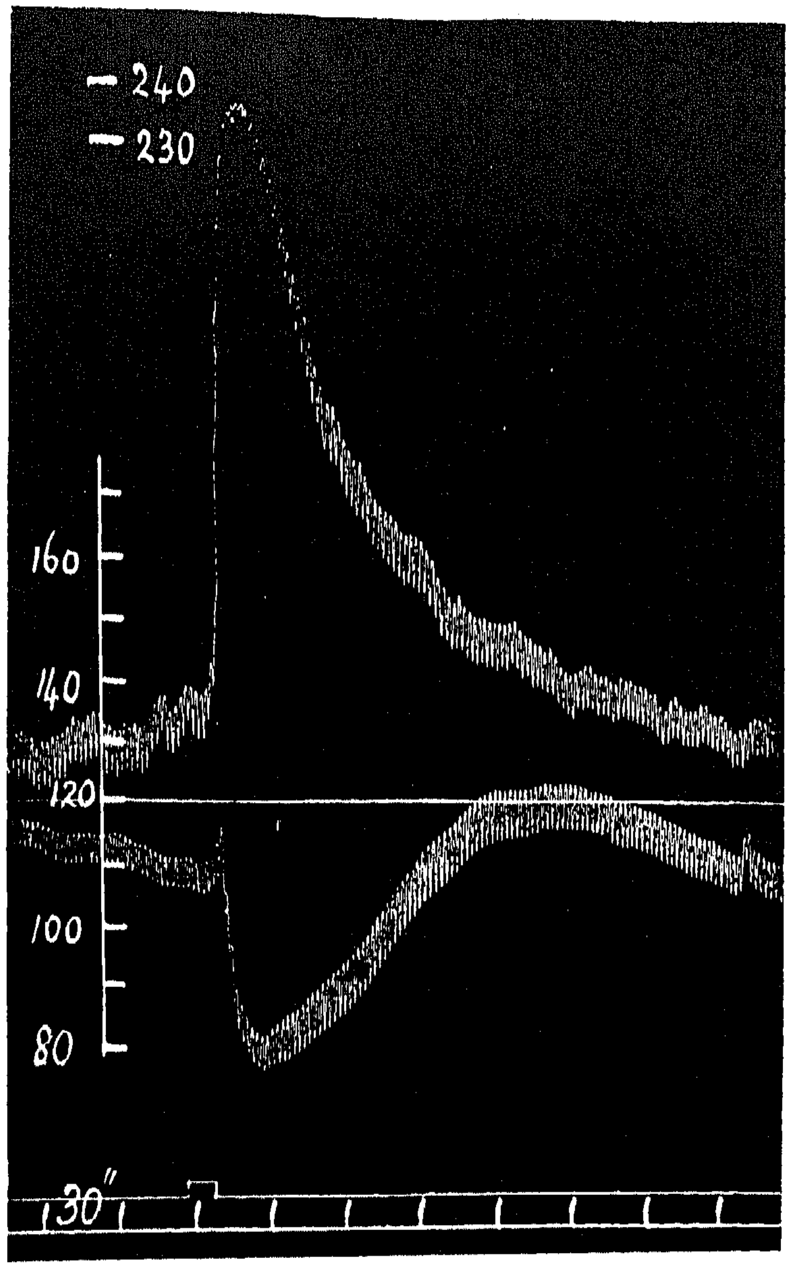


FIG. 34-2. The effect of epinephrine on the blood pressure of the pithed cat before and after ergotamine.

The *upper curve* was produced by 0.025 mg. of epinephrine and the *lower curve* by 0.1 mg. of epinephrine after 10 mg. of ergotamine. (From Dixon, *Manual of Pharmacology*, Edward Arnold & Co., 1936.)

## Absorption.

Epinephrine is very poorly absorbed from the gastrointestinal tract. Little evidence of pharmacologic response results from the oral administration of the drug at the usual dosage level. The absorption of epinephrine is prompt from the depot of a subcutaneous injection. The vasoconstriction elicited by the drug at the injection site diminishes its absorption rate. This interference with absorption through vascular constriction is less when the injection is made intramuscularly. The promptness of action upon subcutaneous injection may be increased by massage of the skin at the injection site.

Intravenously epinephrine produces a prompt and intensified response. The intravenous dose is from $1/60$ to $1/25$ of the subcutaneous dose. It is therefore important to be certain that upon intramuscular injection of the drug it is not injected into a small vein.

Klinefelter (1937) developed the use of epinephrine sprays in the treatment of bronchial asthma. The official solution of 1 per cent of epinephrine hydrochloride is used in a suitable nebulizer. The mouth is opened wide and the solution is sprayed into the throat. Excellent bronchiolar relaxation promptly results, and the necessity of a parenteral injection is avoided. The success of this procedure is largely dependent upon the efficacy of the nebulizer in producing an aerosol of the epinephrine solution.

The absorption of epinephrine is prompt from the nasal membrane when used in the form of a spray. Its vasoconstrictive properties, however, confine the action to the local area.

**Toxicity.**

Epinephrine has frequently produced death because of overdosage caused by errors in the preparation of solutions or by the administration of a subcutaneous dose intravenously. Deaths from epinephrine poisoning are generally the result of dosage errors. The fatal subcutaneous dose in man is approximately 10 mg. (10 ml. of a 1:1000 solution). The symptoms of poisoning are:

Tachycardia and palpitation
Dyspnea and severe headache
Pallor and pupillary dilatation
High blood pressure and rapid collapse

Death is generally caused by acute cardiac dilatation, ventricular fibrillation, and pulmonary edema. In elderly individuals with hypertension, death may be caused by a vascular accident. Caution should be used when the drug is employed in debilitated individuals and in persons with hypertension, angina pectoris, or other cardiac involvements. In chloroform and cyclopropane anesthesias its use is strictly interdicted (see pages 321 and 323).

**Therapeutic uses.**

The therapeutic uses of epinephrine are numerous, and many of these have been discussed in the foregoing paragraphs. The principal therapeutic uses of the drug are summarized below.

One of the principal clinical applications of epinephrine is in the *treatment of bronchial asthma.* Through the stimulation of the effector cells of the adrenergic nerves which are relaxant to the bronchial musculature, the bronchioles are dilated and the asthmatic attack is terminated. The official 1:1000 injection, 0.1 to 0.5 ml. subcutaneously, is often used. Also the oil solution, 1:500, is used intramuscularly to prolong the duration of action. By means of a nebulizer the 1:100 official solution is sprayed directly into the throat. This affords prompt relief and is widely used.

Epinephrine is employed in the treatment of *urticaria, angioneurotic edema,* and *serum sickness.* The effects of the drug are prompt, and frequently the improvement of the patient is dramatic. For this purpose 0.5 to 1 ml. of the 1:1000 official solution is used subcutaneously or intramuscularly.

Epinephrine in saline solution is extensively employed in the form of a nasal spray for *shrinkage* of the *mucous membrane* prior to a nasal examination and for preparation for nasal surgery. It is also used to enlarge the nasal air passage when it is narrowed by turgescence of the turbinates in hay fever, rhinitis, and sinusitis. For this purpose aqueous solutions 1:10,000 to 1:1,000 are used, and oil solutions 1:1,000 are valuable to prolong the action of the drug.

The vasoconstricting action of epinephrine is useful to check *local hemorrhage.* The official 1:1000 solution is employed for this purpose. It is very successful in checking *epistaxis.*

Epinephrine is a frequent constituent of collyria. It is often used with zinc sulfate and boric acid; the strength is usually 1:10,000. It is of value as a decongestive agent in *conjunctivitis* and *blepharitis.*

In *acute cardiac arrest* epinephrine has been found to be useful. If the heart is still beating, the drug is injected directly into the jugular vein (0.05 to 0.1 ml. of the official 1:1000 solution diluted to 5 ml. with normal salt solution). If the heart is stopped, 0.5 to 1 ml. of the 1:1000 solution is promptly injected directly into the right atrium (see page 542).

Because of its vasoconstricting action epinephrine is used to prolong the action of local anesthetics. It prevents their rapid absorption from the site of injection. A solution 1:100,000 to 1:10,000 is used for this purpose.

### Norepinephrine

Norepinephrine or arterenol is an established therapeutic agent. This compound was identified in suprarenal medullary extracts. von Euler (1950) showed that norepinephrine is a specific neurohormone of the adrenergic nerves. This substance is selectively released from the adrenal medulla upon hypothalamic or reflex stimulation. The conditions for release of the hormone and its physiologic functions correlate well with the action of norepinephrine as a pharamcologic agent.

As with epinephrine the levo-isomer of norepinephrine is the more active and is hence the agent used therapeutically. The term *norepinephrine* is derived from the German expression "Nitrogen ohne Radikal," referring to the fact that the molecule is identical with that of epinephrine, except that the methyl group on the nitrogen

atom is absent. The major pharmacologic differences between the two compounds are discussed below.

In intact dogs and cats *l*-norepinephrine appears to be from 1 to 4 times more active as a pressor agent than *l*-epinephrine. Adrenergic blocking compounds which reverse the vasopressor response of epinephrine do not reverse, but usually only reduce the pressor response of norepinephrine.

In normal human subjects the intravenous infusion of 0.4 μg./kg./min. of *l*-norepinephrine produced reflex bradycardia. Epinephrine elicited tachycardia, apprehension, and restlessness. The subjective symptoms observed after norepinephrine were insignificant. Epinephrine, on the other hand, evoked mild palpitation, hyperventilation, tightness of the chest, and muscular fatigue.

Lever *et al.* (1961) infused intravenously into an antecubital vein of young adult persons 10 to 30 μg./min. of norepinephrine. There was an initial rise in blood pressure and a decline during the infusion. After the infusion was discontinued, the blood pressure fell below the base line, with subsequent rise to the base line level. Using dogs and rabbits they demonstrated that vasodilatation occurs in skeletal muscle and the intestine during the latter stages of the infusion. They suggest that this may be in part responsible for the secondary depressor response. Also they propose the possibility of the production of a vasodilator substance induced by the intravenous injection of norepinephrine.

Norepinephrine increases the oxygen consumption and the minute volume of the heart to a much smaller extent than does epinephrine. Cotten and Pincus (1955) studied the positive inotropic effect of epinephrine and norepinephrine on the dog's heart by means of the strain gauge arch. The effects were qualitatively and quantitatively similar over a wide dosage range. The rise in blood pressure produced by each of the substances was associated with an increase in the force of ventricular contraction.

Isolated segments of the small intestine are relaxed by norepinephrine. The relative relaxant action of the two hormones varies with different species.

The isolated guinea pig's uterus is inhibited by norepinephrine and epinephrine. From 2.5 to 10 times more norepinephrine is required than epinephrine.

Bronchospasm in various species is combated by norepinephrine, although it is much less effective than epinephrine.

The acute toxicity of norepinephrine is less than that of epinephrine. Melville and Shister (1959) demonstrated that norepinephrine was less injurious to the normal and arteriosclerotic rabbit heart than epinephrine.

The *d*- and *l*-norepinephrines qualitatively elicit the same response. However the *d*-isomer exerts only a small fraction of the activity of *l*-norepinephrine.

The marked effect of norepinephrine as a cerebral hormone affecting behavior is discussed on page 494.

**Levarterenol Bitartrate, U.S.P. (Levophed Bitartrate).**

Levarterenol bitartrate occurs as a white crystalline powder which is freely soluble in water. The pH of a 0.1 per cent solution is between 3 and 4. One mg. of the bitartrate is the equivalent of 0.56 mg. of the base.

Levarterenol bitartrate is used to elevate the blood pressure in hypotensive states resulting from trauma, hemorrhage, central vasomotor depression, and acute myocardial infarction. For this purpose levarterenol possesses a wider margin of safety between its pressor and toxic doses than does epinephrine. The intravenous infusion of levarterenol produces bradycardia instead of tachycardia, as is produced by epinephrine. The bradycardia appears to be of vagal origin and may be blocked by the previous administration of atropine. Like epinephrine, levarterenol sensitizes the myocardium to arrhythmias and ventricular tachycardia when the subject is under cyclopropane anesthesia.

Levarterenol bitartrate is administered by intravenous infusion. It is dissolved in normal salt solution, 5 per cent dextrose solution, plasma, or whole blood. The recommended concentration is 4 μg. of base/ml. This is prepared by adding 4 ml. of a 0.2 per cent solution of the bitartrate (equivalent to 0.1 per cent of the base) to each liter of fluid to be infused. The average dose varies from 5 to 20 μg. of the base (1.25 to 5 ml. of the dilution) per minute. It may be necessary to use larger doses, in a more concentrated solution, in some cases. Indeed as much as 100 mg. may be given in the course of a day without toxic effects. Careful checks of the blood pressure are essential at 2- to 5-minute intervals to avoid dangerous hypertensive effects.

The intravenous infusion of levoarterenol must be carried out with special precautions to avoid the inadvertent extravasation of the solution into the tissues. Soft tissue sloughs are frequently caused by the action of the drug. Infiltration into the tissue after long intravenous infusion presents a similar hazard. Phentolamine has been recommended to prevent sloughs and necrosis (Zucker, 1957). Other sympathomimetic amines such as metaraminol bitartrate (Aramine) have produced similar tissue damage (Shaub, 1960).

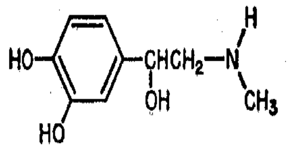
Levarterenol is also used as a vasoconstrictor with local anesthetics. Spinal anesthesia is prolonged by the use of levarterenol with the spinal anesthetic agent.

### EPHEDRINE

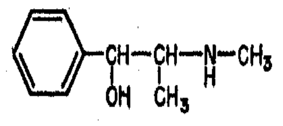
Ephedrine is an alkaloid obtained from *Ephedra equisetina*, *Ephedra sinica*, or other species of *Ephedra*. It is also prepared synthetically. The alkaloid was isolated first by Nagai in 1887. The Chinese plant "ma-huang" from which it was obtained had been used in oriental medicine for centuries. The capacity of the alkaloid to dilate the pupil was observed by Takahashi and Muira (1888). They used a 10 per cent solution of the compound by instillation into the conjunctival sac and observed wide pupillary dilatation in several species of animals and in man.

The use of the drug in occidental medicine stems from the observation of Chen (1924), who found that an extractive preparation of Ephedra, which was alleged to possess therapeutic merit by a Chinese apothecary, elicited an epinephrine-like rise on the blood pressure. The classic researches of Chen *et al.* (1924 to 1929) were responsible for the exploration of the pharmacology and therapeutic applications of ephedrine. Their work established the drug in clinical medicine and served as an impetus for chemical and pharmacologic research among the homologs and analogs of epinephrine.

The relation of the chemical structure of ephredrine to epinephrine may be observed from the accompanying formulas.



Epinephrine
(Methylaminoethanol Catechol)



Ephedrine
(Phenylpropanol Methylamine)

It will be observed that although epinephrine is a catechol derivative with 2 hydroxyl groups on the benzene ring, ephedrine is a phenyl derivative. Furthermore, the alkyl side chain of ephedrine contains an extra carbon atom in addition to the 2 present in the ethanol group in epinephrine.

Ephedrine extracted from the *Ephedra* plants is *l*-ephedrine. This is the product recognized by the United States Pharmacopeia. Since the molecule of ephedrine contains 2 asymmetric carbon atoms, there are 4 possible isomeric ephedrines. Chen *et al.* (1929) studied the pharmacologic activity of the ephedrine isomers. Their data clearly indicate the importance of the spatial relationship of the atoms in the molecule of this sympathomimetic amine. *l*-Ephedrine and *dl*-ephedrine are by far the most potent, whereas *l*-pseudoephedrine and *dl*-pseudoephedrine are quite devoid of pressor activity in the test animal.

The Pharmacopeia recognizes *l*-ephedrine base, which is an unctuous, almost colorless solid. It is soluble in oil and water. The hydrochloride and sulfate of *l*-ephedrine are also official. These are white, crystalline, soluble salts. Racemic ephedrine, in the form of its hydrochloride, is recognized in *New and Nonofficial Drugs* under the name of *Racephedrine hydrochloride*.

### Pharmacologic responses to ephedrine.

**Effect on the circulation.** Upon intravenous injection ephedrine, like epinephrine, produces a prompt rise in blood pressure. The potency of ephedrine is from 0.005 to 0.01 of the potency of epinephrine as a pressor. Its duration of action, however, is from 7 to 10 times as long as that of epinephrine.

The pressor response of the two drugs in equipressor doses is shown in figure 34-3.

In addition to the difference in duration of response, there are many other interesting pharmacologic differences between the pressor action of ephedrine and of epinephrine. These are listed as follows:

The pressor response of ephedrine is not potentiated by the previous injection of cocaine. It is not obliterated or reversed by ergotamine.

Repetitious injections of ephedrine produce tachyphylaxis, as shown by a diminution of pressor response.

K. K. CHEN

*Distinguished American pharmacologist whose work led to the use of ephedrine in medicine*

"Quality work takes the combination of skill, experience, efficiency, and ingenuity."

The pressor response to ephedrine is evoked upon oral administration.

The coronary vessels are dilated by ephedrine.

The myocardium is not directly stimulated by ephedrine, but probably only through its action on the cardiac accelerator mechanism.

**Response of the central nervous system.** Ephedrine directly stimulates the respiratory centers. This action is not shared by epinephrine. This action of ephedrine is of value in combating respiratory depression caused by various central nervous system depressant drugs. The sensory areas of the cerebral cortex are stimulated by ephedrine; this action likewise is not elicited by epinephrine. Other sympathomimetic amines, such as amphetamine, are more powerful cerebral stimulants than ephedrine (see page 475).

**Effect upon the bronchioles.** Like epinephrine, ephedrine dilates the bronchiolar musculature. The action is mediated through the stimulation of the effector cells of the adrenergic fibers, which are relaxant to the bronchioles. Although

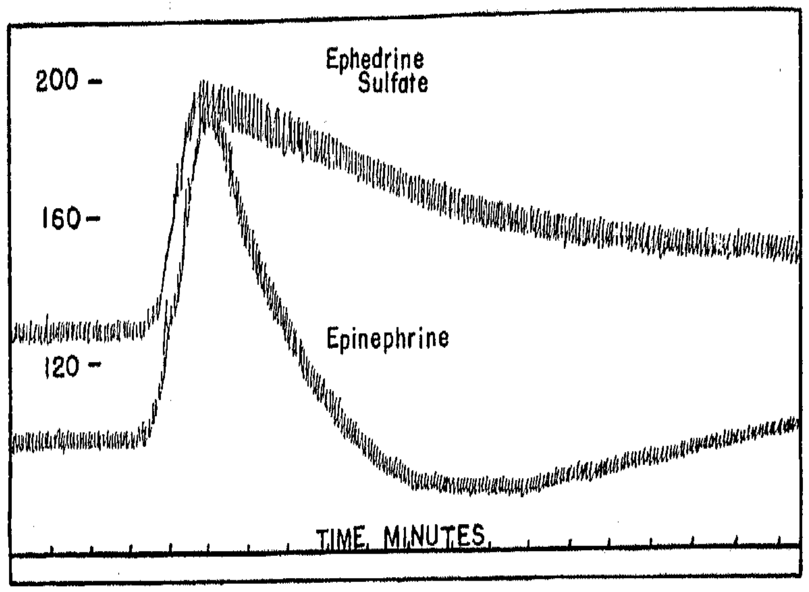


FIG. 34-3. The effect of ephedrine and epinephrine on the blood pressure of the pithed cat upon intravenous injection.

the action of ephedrine in asthma is not so prompt or effective as that of epinephrine, it has the advantage of being active upon oral administration. In addition, its action is of longer duration. Also it is excellently suited for routine prophylactic therapy in the asthmatic patient.

For prompt action in asthma 25 mg. of ephedrine sulfate or hydrochloride may be given subcutaneously. When given orally the drug's action is slower. The oral dose is 25 to 50 mg. Ephedrine has an advantage over epinephrine in the treatment of asthma in individuals where the asthmatic state is complicated with diabetes. The hyperglycemia produced by ephedrine is far less marked than that elicited by epinephrine.

Most of the sympathomimetic amines share the bronchodilator action of epinephrine.

Cameron and Tainter (1936) found that 0.02 to 0.04 mg./kg. of epinephrine was effective and that 1 to 3 mg./kg. of ephedrine produced only moderate bronchodilatation.

Pseudoephedrine, as stated previously, is a stereo-isomer of ephedrine which evokes only a minor activity on the circulation. However, its action on the bronchioles is equal to that of ephedrine. This isomer of ephedrine is available under the name of *Sudafed* and is indicated in the various conditions in which ephedrine is employed. Its action appears to be as dependable as that of ephedrine, but its adverse side effects are fewer in number and less in degree (Brown, 1959).

**Effect upon the eye.** Systemically as well as locally ephedrine produces pupillary dilatation. The dilatation is active and not passive, as is that produced by atropine. The mydriasis is mediated through the stimulation of the effector cells in the radial muscle of the iris, which are innervated with adrenergic fibers. Cycloplegia is not produced with mydriasis because the action of ephedrine does not involve the ciliary nerves. The mydriasis is produced by action of ephedrine in the effector cells, since it persists after the severance of the cervical sympathetic nerves and their subsequent degeneration.

Chen and Poth (1929) found that the mydriasis of ephedrine occurred in the Caucasian race but not in the Ethiopian. The degree of pupillary dilatation in the Mongolian is intermediate between these extremes. This difference is apparently not related to iris pigmentation, for the mydriasis is the same in gray rabbits as it is in the albino animal.

The pupillary dilatation produced by the instillation of a 10 per cent solution of ephedrine sulfate into the conjunctival sac is used for the opthalmoscopic examination of the eye grounds.

**Effect on skeletal muscle.** Ephedrine increases the tone of skeletal muscle and for this reason is used in the treatment of myasthenia gravis (see page 588). Epinephrine evokes a decurarizing action on skeletal muscle. Ephedrine appears to inhibit the enzymic destruction of epinephrine and prolongs its decurarizing action.

**Local action on the nasal membranes.** Like epinephrine, ephedrine solutions are active as nasal *decongestives*. The topical application of ephedrine hydrochloride or sulfate solutions (1 to 1.5 per cent) to the nasal membranes constricts the capillaries to a moderate degree and thus diminishes hyperemia. Turgescence is reduced, and the airway patency is established. Ephedrine is less prompt in its action as a decongestive than epinephrine, but its action is more sustained. In addition, the drug is well tolerated upon repeated application. Side effects are rare.

**Fate in the body.** It has been shown by Axelrod (1953) that after intraperitoneal injection into dogs of solutions of ephedrine salts, 80 per cent was excreted in the urine as norephedrine (Propadrine). About 1 per cent was excreted as *p*-hydroxy-norephedrine and about 0.3 per cent as *p*-hydroxyephedrine. The demethylation of ephedrine is rapid, 60 per cent occurring in the first hour. When norephedrine was administered, most of the compound was excreted in the urine unchanged. It appears from these studies that extended pressor and other responses elicited by ephedrine are produced partly by the metabolite norephedrine.

### Therapeutic uses.

Ephedrine is used topically as a nasal decongestive. For this purpose solutions of the salts of the alkaloid in normal saline solution 1 to 1.5 per cent are used. To prolong the action a 1 per cent solution of the alkaloidal base in oil is also used.

Ephedrine is used routinely in the treatment of *asthma*. Capsules and tablets of 25 to 50 mg. are available. These are administered 3 or 4 times daily. The drug is also available for subcutaneous administration. Repeated use of ephedrine, especially in women, has given rise to *subjective tremors of the extremities*. The effect is not, however, serious and generally disappears immediately when the drug is discontinued.

Ephedrine sulfate solution, 10 per cent, is used locally to produce *mydriasis* for routine ophthalmoscopic examination of the eye grounds.

Ephedrine is used to increase *muscle tone* in *myasthenia gravis* (see page 588).

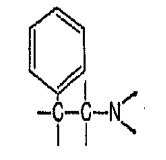
Ephedrine has had a wide use in the treatment of *bronchial coughs*. It provides a greater patency of the bronchioles and tends to relieve the accompanying dyspnea.

### OTHER SYMPATHOMIMETIC AMINES

The large class of amines which mimic the action of norepinephrine and/or epinephrine on the effector cells of the sympathetic division of the autonomic nervous system is called the *sympathomimetic amines*. They comprise a large number of compounds, many of which have warranted continued therapeutic use. The alkaloids ephedrine and amphetamine, which have been discussed previously, are typical members of this class. The organic chemist has sedulously explored the possibilities in this field, and with numerous compounds of related structure available, the relationship between chemical constitution and pharmacologic response has been extensively investigated.

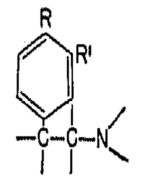
For purposes of this discussion these compounds will be classified into the following categories.

1. Those compounds containing the phenyl group with the following type structure:



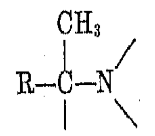
To this group belong *ephedrine*, *amphetamine*, *Propadrine*, *Vonedrine*, *Norodin*, and others.

2. Those compounds containing the phenol or catechol nuclei with the following type structure:



R and R¹ are hydroxyl groups. With both hydroxyl groups on the ring, epinephrine, cobefrine, and norepinephrine fall into this class. When one hydroxyl group is on the ring *para* to the side chain, we have *Synephrine* and *Paradrine*. When the hydroxyl group is *meta* to the side chain, phenylephrine is formed.

3. Those compounds in which an open chain aliphatic hydrocarbon has been substituted for the aryl nucleus are represented by the general type structure:

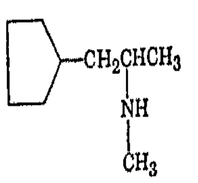


$$\mathrm{R{-}\overset{\overset{CH_3}{|}}{\underset{|}{C}}{-}N\langle}$$

In the formula R represents a saturated or unsaturated straight chain hydrocarbon containing 5 or 6 carbon atoms. *Tuamine* (2-aminoheptane), *Octin* (methylisooctenylamine), and *Forthane* (methylhexamine) belong to this class.

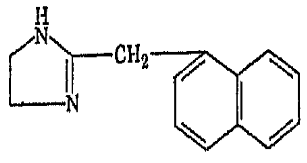
4. Those compounds containing a cyclic nucleus other than phenyl. In this class belongs

clopane (1-cyclopentyl-2-methylamino propane). The structure is shown in the accompanying formula.



Clopane

5. Those compounds containing cyclic nuclei other than phenyl or substituted phenyl with the aliphatic side chain closed, of which one clinically useful compound in this class, namely, *Privine hydrochloride* or 2(1-naphthylmethyl) imidazoline hydrochloride (see formula).



Privine

The following relationships between chemical constitution and pressor response hold in general among these compounds.

1. By increasing the number of carbon atoms in the aliphatic side chain from 2 to 3 and removing the 2 phenolic hydroxyl groups, pressor activity is diminished but duration of action is increased (ephedrine). By increasing the length of the aliphatic side chain beyond 3 carbon atoms, pressor response is diminished and toxicity is increased.
2. Alcoholic hydroxyl groups in the aliphatic side chain increase the pressor activity, as in the catechol derivative (norepinephrine).
3. Methylation of the amine group diminishes pressor response (N-methylepinephrine).
4. Hydroxyl group substitution on the benzene nucleus enhances pressor activity (phenylephrine).
5. Substitution of the phenyl group by an open chain hydrocarbon effects diminution in pressor response (tuamine).
6. Siegmund *et al.* (1948) observed that saturation of the phenyl ring to produce cyclohexyl isopropylamines results in compounds with prolonged pressor effects upon oral administration. The intravenous pressor action of the saturated compound is less than that of the phenyl.
7. By replacement of the methyl group on the nitrogen atom in epinephrine by an alkyl group such as isopropyl, the inhibitory action of epinephrine is enhanced, and the compound exhibits marked vasodepressor activity. This is manifested in *isoproterenol (Isuprel)*, which is 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol. However, this modification of the molecule enhances the effect on the cardiac accelerator mechanism.

In table 34-1 there is a list of several commonly used sympathomimetic amines. Their chemical constitution and their pressor potencies are compared with epinephrine.

## Choice of Sympathomimetic Amines in Therapy

The sympathomimetic amines are very popular and useful drugs. Their manifold therapeutic applications have been exemplified in the use of epinephrine (see page 548), norepinephrine, and ephedrine (see page 553). It is estimated that this class of medicaments is prescribed in 10 per cent of physicians' prescriptions. In addition, some are ingredients in popular nasal decongestants.

A consideration of the amines listed in table 34-1 is therefore important from the point of view of selection of a *drug of choice* for specific therapeutic purposes.

For the treatment of the *asthmatic patient*, *epinephrine* still appears to be one of the most prompt and dependable drugs. Its availability as an aerosol in 1:100 solution has widened its field of usefulness. *Isoproterenol hydrochloride* (Isuprel hydrochloride) is gaining favor in the treatment of asthma. It sometimes succeeds where epinephrine fails. It is available in tablets of 10 and 15 mg. for sublingual use. It is employed also by inhalation in nebulizers and inhalers. The compound enjoys a wide margin of safety as a therapeutic agent.

In *acute cardiac arrest*, *epinephrine* is the drug of choice (see page 548).

In *urticarial conditions*, *epinephrine* appears to be still the preferred drug of this group. Although sympathomimetic amines, such as ephedrine, are valuable, epinephrine remains the drug of choice.

For *central stimulation*, *d*-amphetamine (*Dexedrine*) is the most useful of all of the sympathomimetic amines. The central nervous system action and use of these drugs are discussed on page 477. Ephedrine shares this central stimulating action to a lesser extent.

TABLE 34-1

*Comparative Activity and Chemical Constitution of Sympathomimetic Amines*

| Name | Chemical Constitution | | Pressor Potency Compared to Epinephrine as Standard | Duration of Pressor Response Compared to Epinephrine as Standard | Bronchodilatation in the Dog with Histamine Bronchial Spasm* | Strength of Solution Recommended as Decongestive | Oral Dose Available in Inhaler† |
|---|---|---|---|---|---|---|---|
| | Carbon cycle or chain | Amine side chain | | | | | |
| Epinephrine, adrenaline | Catechol | Ethanol-methylamine | 1 | 1 | ++++ | 1:10,000–1:1,000 | — |
| Arterenol, norepinephrine (Levophed) | Catechol | Ethanolamine | 1–4 | 0.5–1 | +++ | Not available | — |
| Neosynephrine, phenylephrine | Phenol | Ethanol-methylamine | 0.2 | 2 | ++ | 1:400–1:200 | — |
| Ethylnorsuprarenin (Bronkephrine) | Catechol | Butanolamine | No increase in systolic B.P. | | +++ | Not available | — |
| Ephedrine | Phenyl | Isopropanol-methylamine | 0.005–0.01 | 7–10 | + | 1:100 | —<br>25 mg. |
| Propadrine | Phenyl | Isopropanol-amine | 0.003–0.017 | 7 | | 1:100 | —<br>25 mg. |
| Amphetamine Benzedrine | Phenyl | Isopropyl-amine | 0.002–0.01 | 5–10 | + | 1:100 | +<br>10 mg. |
| Vonedrine | Phenyl | Isopropyl-methylamine | 0.003–0.01 | 5–10 | + | 1:100 | + |
| Tuamine | Heptyl | Amine | 0.003 | | | 1:200–1:100 | + |
| Privine Naphazoline | Naphthyl-ene | Methyl-imidazoline | 0.2 | 4–6 | | 1:2000–1:1000 | — |
| Clopane | Cyclopentyl | Isopropyl-methylamine | 0.005 | 7–10 | | 1:200 | — |
| Forthane | 4-Methyl-hexane | Amine | 0.004 | 6.8 | | | + |
| Methoxyphenamine (Orthoxine) | *o*-Methyoxyphenyl | Isopropyl-methylamine | 0.0005–0.005 | 2 | +++ | Not available | —<br>50 mg. |
| Isoproterenol, aludrine (Isuprel) | Catechol | Ethanol-isopropylamine | No increase in systolic B.P. | | +++ | 1:200–1:100 | +<br>15 mg. |
| Sympatol, synephrine | Phenol | Ethanol-methylamine | 0.03 | 2–3 | | | +<br>100 mg. |
| Methoxamine (Vasoxyl) | Dimethoxy-phenyl | Isopropanol-amine | 0.02 | 20–40 | | 1:200 | — |
| Benzedrex | Cyclohexyl | Isopropyl-methylamine | 0.03 | | | | + |
| Paredrine Hydroxyamphetamine | Phenol | Isopropyl-amine | 0.01 | 6–20 | | 1:1000–1:100 | —<br>20 mg. |
| Oenethyl | Heptane | 2-Methyl-amine | | | | 1:100 | — |
| Mephentermine (Wyamine) | Phenyl | Tertiary butyl-methylamine | 0.01 | 3–5 | | | +<br>25 mg. |
| Metaraminol bitartrate (Aramine) | Phenol | 2-Amino-1-propanol | 0.05 | 7–10 | | 1:400–1:200 | — |

* Degree of activity.

† Not available in this dosage form.

As *decongestives* in nasal congestion accompanying *acute and chronic rhinitis*, *vasomotor rhinitis*, and *rhinosinusitis*, it is our opinion that *phenylephrine* and *clopane* are the drugs of choice. Their decongestive action is prompt. Prolonged and repeated application does not give rise to irritation and turgescence of the nasal membranes as is sometimes caused by epinephrine.

For use as *ophthalmic decongestants*, *phenylephrine* and more recently *Visine* appear to be the drugs of choice. Menger (1959) found Visine (tetrahydrozoline) most effective in the treatment of conjunctival irritation. It is active in very low concentrations (0.05 per cent) and evokes no side effects beyond a mild transient irritation (see page 248).

For *pupillary dilatation* for routine ophthalmoscopic examination of the eye grounds, *ephedrine sulfate* appears to be the drug of choice. Its 10 per cent solution has served effectively in this capacity for many years.

For repetitious use in an inhaler, it is our opinion that *Benzedrex* and *Forthane* are the preferred drugs. With many of the sympathomimetic amines containing the phenyl group, susceptible individuals experience a stimulation of the cough reflex after inhalation. Benzedrex and Forthane appear to provoke this effect less than many other agents. Besides, their pressor activity is minimal.

To combat the acute fall in blood pressure during *spinal anesthesia*, *phenylephrine*, *norepinephrine*, and *mephentermine* are favored.

In *myasthenia gravis*, *ephedrine* is the drug preferred. Amphetamine has been used, but ephedrine appears to be the most useful of this class of drugs in myasthenia.

In *vasomotor failure* and *cardiogenic shock* presenting acute hypotension, *norepinephrine*, levarterenol bitartrate, as the natural vasoconstrictor agent is the drug of choice. Phenylephrine 0.1 to 1 ml. of a 1 per cent solution is also employed.

For the treatment of heart block *isoproterenol* (Isuprel) is extensively used and appears to be the sympathomimetic amine of choice (see page 662).

*Vasoxyl* (methoxamine hydrochloride) has been found useful in reestablishing *normal sinus rhythm* and *reducing cardiac rate*. Most sympathomimetic amines evoke a tachycardia; Vasoxyl causes a slowing of the sinus rhythm. The mechanism of action appears to be mediated through the reflex stimulation of the vagus. Brill *et al.* (1959) demonstrated that Vasoxyl was capable of suppressing experimentally-induced ventricular arrhythmias in dogs for periods of 30 to 60 minutes. Since the ventricles are not innervated by the vagus, this action of Vasoxyl must be mediated through a different mechanism. Gilbert *et al.* (1958) observed that Vasoxyl prolongs the action potential, prolongs the absolute refractory period, raises the threshold to stimulation, and slows the A-V conduction. This action of the drug on the myocardium offers an explanation for its anti-arrhythmic activity.

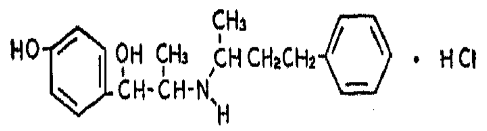
Accordingly, Brill *et al.* (1959) confirmed this action of Vasoxyl in a series of patients with arrhythmias of various origins. They reported that intravenous Vasoxyl in single doses of 10 to 20 mg. was capable of suppressing clinical arrhythmias for periods of 20 to 40 minutes.

*Mephentermine* (*Wyamine*) is favored in combating *hypotensive states* in cardiogenic shock. Glassman and Seifter (1954) studied mephentermine and certain other sympathomimetic amines on the isolated perfused frog heart. Mephentermine was observed to be more potent than epinephrine, norepinephrine, amphetamine, desoxyephedrine, and ephedrine in restoring the contractility of the depressed or hypodynamic heart. Mephentermine was capable of preventing or terminating epinephrine-induced arrhythmias in the dynamic and hypodynamic heart.

For localizing the action of *local anesthetic agents*, *epinephrine* is probably used more than any other of the sympathomimetic amines. However, norepinephrine is gaining favor; although a higher concentration is required, it has the advantage of producing no side effects. Phenylephrine is also used for this purpose.

## NYLIDRIN HYDROCHLORIDE, N.F. (ARLIDIN)

The drugs most generally used to produce peripheral vasodilatation in peripheral vascular disease are the adrenergic blocking agents (see page 561). However, certain adrenergic agents produce vasodilatation and have been found useful in therapy. Arlidin is such a compound. The structure of Arlidin is shown in the following formula:



Nylidrin Hydrochloride
Arlidin
[1-(*p*-hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)propanol hydrochloride]

Arlidin is a white, crystalline powder which is sparingly soluble in water.

### Pharmacologic response to Arlidin.

Arlidin, when administered orally or parenterally to laboratory animals, causes an increase in cardiac output, increased peripheral blood flow to the skin and muscles, and a slight decrease in mean arterial pressure. The peripheral vasodilating action of Arlidin and depressor response appear to occur via a sympathomimetic inhibitory pathway rather than through the process of adrenergic blockade (Schäffer and Kühle, 1952).

The acute and chronic toxicity of Arlidin was found to be of a low order. The oral $LD_{50}$ in mice is greater than 250 mg./kg. (Freedman, 1955). The chronic oral feeding to dogs produced no significant changes in the blood picture or viscera of the animals. The compound appears to be slowly metabolized in the body.

### Clinical use of Arlidin.

Arlidin is indicated in vascular disorders of the extremities. It has been used successfully in intermittent claudication, diabetic vascular disease, Raynaud's disease, Buerger's disease, and night leg cramps. Pomeranze *et al.* (1955) obtained good results in intermittent claudication in a limited series of cases. Their observations were controlled by placebo therapy.

DeCrinis *et al.* (1959) demonstrated that increased blood flow in the extremities produced by exercise was further augmented by the intravenous injection of 7 mg of Arlidin. The enhanced blood flow response prevailed in normal subjects and in patients with nongangrenous occlusive arterial disease of the lower extremities. They concluded that Arlidin apparently increased the capacity of the blood vessels of skeletal muscle to respond to exercise. These observations are in accord with the findings of Caliva *et al.* (1959), who found that Arlidin evoked a 30 per cent increase in blood flow through the calf, but no augmentation of blood flow to the skin. They recorded also an average increase of 34 per cent in cardiac output and a concomitant decrease of 23 per cent in peripheral resistance.

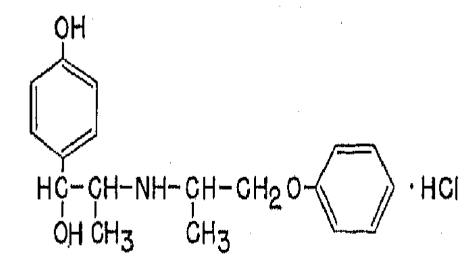
Murphy and Klasson (1957) studied Arlidin in 79 cases of peripheral vascular disease. Their results are set forth as follows: 72 per cent improvement in arteriosclerosis obliterans, 66 per cent in Buerger's disease, 66 per cent in abdominal aortic occlusion, 71 per cent in chronic venous insufficiency, and 50 per cent in elephantiasis. These data compare very favorably with similar studies using the adrenergic blocking agents, which generally evoke more disconcerting side effects. Rubin and Anderson (1958) used Arlidin in a number of cases of labyrinthine arterial insufficiency and found the drug superior to other agents employed to treat circulatory disorders of the inner ear.

The side effects encountered with Arlidin are few. Nervousness and palpitation may occur but usually disappear with continued therapy or reduction of dosage. Arlidin is contraindicated in acute coronary thrombosis.

The drug is available in 6-mg. tablets and in ampules of 5 mg./ml. for parenteral use. The usual oral schedule of dosage is 3 to 6 tablets daily.

## ISOXSUPRINE HYDROCHLORIDE (VASODILAN)

Vasodilan is a hydroxyephedrine derivative, which, like Arlidin, is used in the treatment of peripheral vascular disease. The structure is shown in the formula:



Isoxsuprine Hydrochloride
Vasodilan
[1-(*p*-hydroxyphenyl)-2-(1′-methyl-2′-phenoxyethylamino)-1-propanol hydrochloride]

Vasodilan occurs as a white, crystalline powder which is soluble in water.

### Pharmacologic response to Vasodilan.

Vasodilan was synthesized by Moed and van Dijk (1956), and its pharmacologic properties were studied by investigators in Europe and America (Weikel *et al.*, 1959; Nash *et al.*, 1958). Vasodilan appears to act directly upon smooth muscle, causing relaxation. It exhibits a specificity for the smooth musculature of the blood vessels and the uterus. It is also a mild bronchodilator. Whether the drug acts directly upon the smooth musculature or through specific dilator receptors has not been definitely established. It exhibits only a mild adrenergic blocking action which is not prominently involved in its vasodilating activity.

Upon intravenous injection or oral administration Vasodilan elicits a mild, transient tachycardia. Simultaneously, Vasodilan increases the contractile force of the heart. Kaindl *et al.* (1956) were the first investigators to show that the marked peripheral vasodilating action of Vasodilan was useful in the treatment of peripheral vascular disease. The peripheral vasodilating action was manifested in man without significant tachycardia or hypotension.

### Clinical use of Vasodilan.

Vasodilan is indicated in the symptomatic treatment of peripheral vascular disease such as intermittent claudication, leg pain, coldness and numbness of the extremities, arteriosclerosis obliterans, diabetic vascular disease, Buerger's disease, and thrombophlebitis. Samuels and Shaftel (1959) employed Vasodilan for a period of 7 months in the treatment of 46 patients with arterosclerosis obliterans. They demonstrated objective improvement in 85 per cent of the patients by the study of increased blood flow to the legs, ability to walk a distance without pain, and healing of gangrenous conditions. The dosage schedule was 10 to 20 mg. 3 times a day. Vasodilan may also be given intramuscularly in doses of 5 to 10 mg.

It does appear that sympathomimetic amine derivatives such as Arlidin and Vasodilan are becoming more generally used in peripheral vascular disease and in many cases are to be preferred to the adrenergic blocking agents because their use is accompanied by a minimum of untoward side effects.

Vasodilan has also been used with some success in the treatment of dysmenorrhea and threatened abortion.

The side effects of Vasodilan are mild and few. Palpitation, nausea, vomiting, and dizziness have been encountered. Larger doses may induce tachycardia and precipitous falls in blood pressure in hypertensive patients.

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# 35

# *Sympathetic Division of the Autonomic Nervous System (Adrenergic Blocking Agents)*

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The agents that mimic the action of epinephrine find a wide field of usefulness in therapeutics. The drugs which successfully block the adrenergic transmitter are few. However, they serve as very useful therapeutic agents. These drugs have been referred to as *sympatholytic* and *adrenolytic* agents. As these compounds block rather than "lyse" the catecholamines, epinephrine and norepinephrine, it seems more fitting to designate them as *adrenergic blocking agents.*

In this class of adrenergic blocking agents 5 groups of compounds are considered important. These are:

1. Ergotamine and its dihydro derivatives;
2. Imidazolines, such as *Priscoline* (tolazoline) and *Regitine* (phentolamine);
3. β-Haloalkylamines, such as *Dibenamine* and *Dibenzyline;*
4. Dibenzazepine derivatives, such as *Ilidar;*
5. Benzodioxanes, such as *Benodaine.*

**The nature of adrenergic blockade.** As previously stated, the conventionally used adrenergic blocking agents do not destroy epinephrine or norepinephrine. They do, however, establish an effective blockade in the effector cells innervated by adrenergic nerves against the activity of epinephrine and norepinephrine. Moore *et al.* (1952) showed that if an adrenergic blocking agent is given intra-arterially (femoral artery) sufficient to block or reverse the vasoconstriction produced by 1 $\mu$g. of epinephrine, larger doses of epinephrine may break through the blockade and cause vasoconstriction. However, after the effect of the larger dose of epinephrine has disappeared the blockade still remains effective against the standard dose of 1 $\mu$g. of epinephrine. This indicates competitive antagonism between the 2 agents and the fixation of the blocking agent in the effector cells, which is apparently not displaced by larger doses of epinephrine.

As stated previously, page 533, Ahlquist (1948) proposed 2 sites in the effector cells for adrenergic activity. He referred to these as the alpha and beta receptors. The alpha receptors are postulated to be concerned with the excitatory responses of epinephrine and norepinephrine and other sympathomimetic amines closely related to them chemically. The beta receptors are the sites of the inhibitory responses of these compounds; these are the receptors affected predominantly by isoproterenol. The alpha or excitatory receptors are those most susceptible to the effect of the adrenergic blocking agents. The beta receptors respond to blockade only with massive doses of the adrenergic blocking agents.

Powell and Slater (1958) showed that 1-(3′,4′-dichlorophenyl)-2-isopropylaminoethanol hydrochloride, which is a dichloro analog of isoproterenol, selectively blocked some inhibitory actions of epinephrine and isoproterenol. The dichloro analog is relatively devoid of either inhibitory or excitatory actions at the dosage levels in which it blocked the bronchodilator, vasodilator, and other inhibitory responses to epinephrine. Thus it appears that this substance is capable of occupying the adrenergic receptor sites in certain tissues and blocking these sites so that they cannot be occupied by epinephrine. Thus the dichloro analog possesses affinity for the inhibitory receptor sites, but is devoid of intrinsic activity when occupying these cell receptors.

Not all receptor sites of the adrenergic hormones are blocked by the adrenergic blocking agents. Evans and Smith (1956) extensively studied the sweating process in the horse. Sweating is produced in the horse by the intravenous injection of epinephrine. Seven different adrenergic blocking agents failed to suppress the sudorific effect of epinephrine in the horse.

Further evidence of adrenergic blockade at the receptor mechanism in the effector cells may be cited. The adrenergic blocking agents do not block neuronal transmission over the sympathetic ganglia. They do not influence the stimulation of smooth muscle elicited by drugs which are not sympathomimetic amines, such as acetylcholine and barium salts. The precise nature of the blockade is not clearly understood. The fact that it can be produced by a variety of compounds which have little in common with respect to their chemical structures is puzzling. It is possible that these adrenergic blocking agents displace a prosthetic group in an enzyme necessary for adrenergic response and/or prevent the proper substrate utilization, thus nullifying adrenergic activity.

Evidence appears to be emanating from various sources that indicates the activity of the catecholamines released in the effector sites of smooth muscle, and also blockade of the activity by adrenergic blocking agents, is mediated through cation exchanges. Srórter and Friedman (1961) showed that the adrenergic blocking agent Dibenzylene diminished muscle contractility and cation exchange of the rat's diaphragm. They attribute its action to the effect on cation exchange.

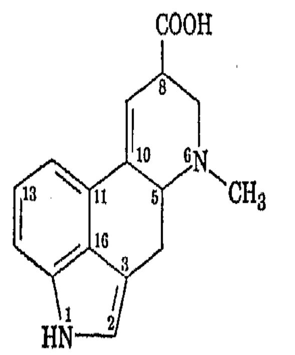
In addition to the foregoing hypothesis concerning the mechanism of adrenergic blockade there remains the possibility of the adrenergic blocking agent affecting the metabolism and/or excretion of the adrenergic hormones. Schapiro (1958) observed that the adrenergic blocking agent Dibenzyline increased the excretion of norepinephrine and decreased the organ content of epinephrine and norepinephrine in the rat. Schapiro suggests that Dibenzyline may interfere with the metabolism of the adrenergic hormones in organs of the body not contiguous to their site of production.

The oldest recognized adrenergic blocking agents are the alkaloids of ergot, namely, ergotamine and ergotoxine. Chemically these 2 alkaloids are closely related. As their pharmacologic actions are essentially the same, we shall confine the discussion to ergotamine, which is used clinically.

### ERGOTAMINE

**Ergotamine Tartrate, U.S.P.** Ergotamine tartrate (Gynergen) is the tartaric acid salt of an alkaloid obtained from ergot. It occurs as colorless crystals or as a white crystalline powder.

One gram of the compound requires 500 ml. of water for solution. Its alcohol solubility is the same as its water solubility. Ergotamine chemically is a derivative of lysergic acid which has the structure shown in the accompanying formula.



Lysergic acid

Upon hydrolysis ergotamine yields:

ergotamine → *l*-phenylalanine + pyruvic acid
+ *d*-proline + ammonia + lysergic acid

Other alkaloids found in ergot are discussed on page 567.

**The response of the central nervous system to ergotamine.** Barger and Dale (1909) showed that ergotamine produced initial stimulation of the central nervous system in animals as manifested by weak clonic convulsions. After the convulsive seizures the predominating symptoms which follow are ataxia, lethargy, fatigue, stupor, and death through the paralysis of the respiratory centers.

**The action of ergotamine on the circulation.** An injection of ergotamine intravenously into various laboratory animals produces a prompt rise in blood pressure. The pressure remains elevated for a considerable period of time. The action of the drug on the blood pressure of the decerebrate cat is shown in figure 35-1.

The effect on the blood pressure as shown in figure 35-1 occurs in the decerebrate animal, which suggests a peripheral effect. The response is elicited after sufficient nicotine has been injected to paralyze the autonomic ganglia. The effect therefore is either directly on the arteriolar musculature or on their constrictor nerves.

Dale observed that with the rise in blood pressure there was a concomitant diminution in organ volume. The pressor action is believed to be due to the action of the drug directly on the arteries. This is augmented by further constriction of the arteries caused by diminished organ volume. Repeated doses of the drug produce decreasing pressor responses.

In an animal that has received repeated doses of ergotamine the excitatory or alpha receptors in the effector cells innervated by the adrenergic nerves to the arterioles are blocked. The beta receptors (inhibitory or relaxant) are not blocked. In the ergotaminized animal (notably the cat) epinephrine evokes a fall in blood pressure (fig. 34-3, page 552).

The pressor response of ergotamine obtained by intravenous injection into laboratory animals is not observed in man after the oral administration of 1 or 2 mg. of the drug.

**The effect of ergotamine on the gastrointestinal tract.** VanLiere and Sleeth (1939) demonstrated that the oral dose to man of 1 mg. of ergotamine delayed the emptying time of the stomach from 16 to 36 per cent. They believed

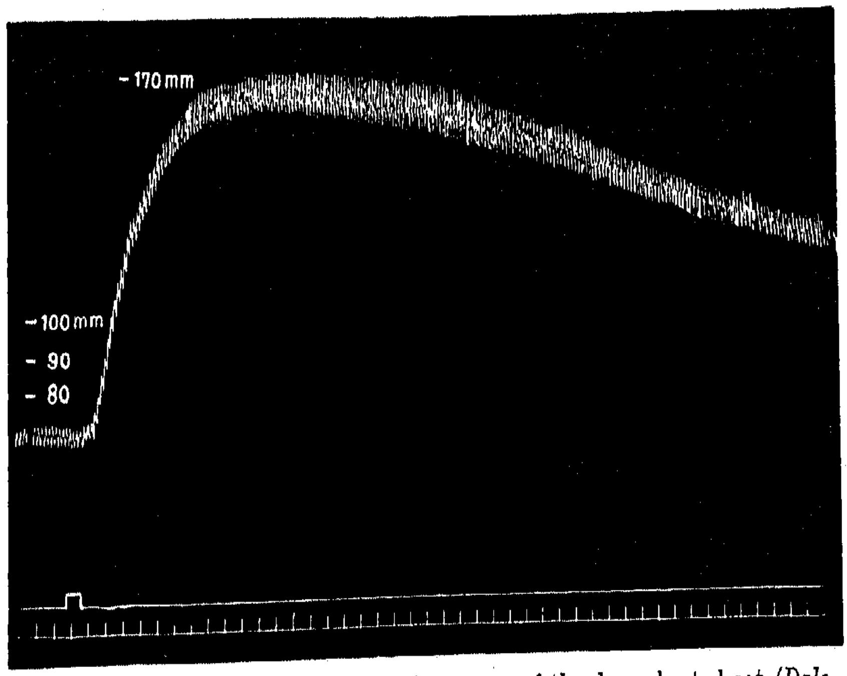


FIG. 35-1. Effect of ergotamine on the blood pressure of the decerebrated cat *(Dale, 1906)*

the action to be due to the direct depressant effect of the drug on the gastric musculature. Owing to the adrenergic blocking action of the drug, peristalsis is generally increased. Increased intestinal motility is observed upon the injection of acetylcholine after the administration of ergotamine. The hyperactivity of the intestinal tract elicited by ergotamine is diminished by atropine.

**The effect of ergotamine on the pupil.** Small doses of ergotamine cause pupillary dilatation. This action is likely mediated through the stimulation of the sympathetic effector cells in the radial muscle of the iris. Larger doses of the drug elicit the adrenergic blocking response, and the pupil is strongly constricted. Dale (1906) and Yonkman (1930) showed that ergotamine affected also the sphincter muscle of the iris. Yonkman found that ergotamine constricts the isolated sphincter muscle of the iris. He believed this action to be direct upon the sphincter muscle and not through the parasympathetic innervation. It appears therefore that ergotamine myosis results from the 2-fold action of adrenergic blocking of the effector cells of the nerves to the radial muscle and also a direct constrictor action on the sphincter muscle of the iris.

**The effect of ergotamine on the uterus.** One of the striking pharmacologic effects of ergotamine is the production of uterine contraction. The drug was used extensively in obstetrical practice prior to the discovery of the more efficient ergot alkaloid *ergonovine*. The uterine musculature is increased in tonus and in the force of its rhythmic contractions. The action is unreliable when the drug is administered orally. Intramuscularly the drug is more dependable, but in effective dosage generally produces undesirable side effects such as nausea and vomiting. The oxytocic action is initiated about 20 minutes after injection and persists for 1 to 2 hours.

Ergotamine elicits its uterine contracting action on isolated uterine strips. Its action is likely mediated through incipient stimulation of the effector cells of the sympathetic motor fibers to the uterus and also through a direct musculotropic action. Like epinephrine, the action of the drug on the uteri of different species is dependent upon the sympathetic motor and inhibitory innervations, page 544.

### THE USE OF ERGOTAMINE IN MIGRAINE

**Migraine.** The migrainous type of headache has been described in medical literature for nearly 2000 years. Aretaeus of Cappadocia (30–90 A.D.) called attention to unilateral paroxysmal head pains accompanied by nausea and emesis. There were remissions of the symptoms and recurrences of the syndrome. He called it *Heterocrania*. Ostfeld (1961) gives an incidence of about 10 per cent in the United States. The frequency in the female is 2½ times that in the male.

Migraine is characterized by periodic, excruciating headache. The headache is often preceded by visual and vasomotor disturbances. Nausea and vomiting frequently occur; the individual may be otherwise completely healthy. The headache may be sharply localized or totally hemicranial. It may extend to the face, neck, shoulders, and arms. There is usually a disturbing sensation of throbbing. The etiology of the disease is not well understood.

**Treatment of migraine with ergotamine.** Maier (1926) suggested the use of ergotamine tartrate in the treatment of migraine. He employed ergotamine for its adrenergic blocking action, based upon the supposition that an overactive sympathetic nervous mechanism was a predisposing factor in migraine.

Ergotamine elicits no analgesia as such in the treatment of migraine. The adrenergic blocking action of ergotamine is not likely responsible for the relief it affords. First, other adrenergic blocking agents are not effective in producing relief. Second, Lennox (1934) observed a patient who had undergone a complete bilateral sympathectomy which did not influence her migraine, but ergotamine promptly aborted each attack.

Graham and Wolff (1937) observed that migraine was related to changes in the amplitude of pulsations of certain branches of the external carotid arteries. They showed that a reduction in the amplitude of pulsations of the temporal artery caused by manual pressure on the common carotid artery produced diminution in the severity of the migrainous pain. Ergotamine tartrate was shown to diminish the amplitude of arterial pulsations to about 50 per cent with a concomitant relief of pain. The effect of ergotamine tartrate on these arterial pulsations is shown in figure 35-2.

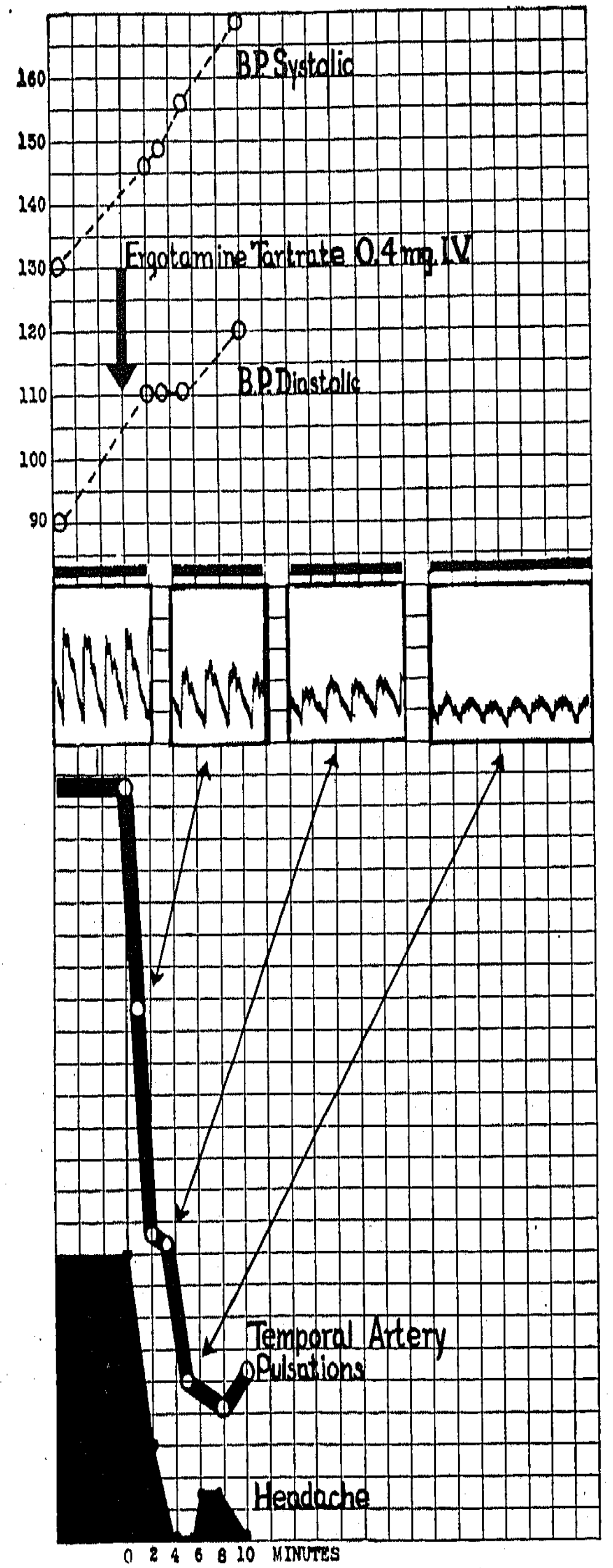


FIG. 35-2. Ergotamine tartrate and pulsation of temporal artery (*Graham and Wolff, 1937*)

Tunis and Wolff (1952) studied further the migraine syndrome. They divided the episode into 3 phases. The first phase shows minimal pulsation amplitude of the external carotid artery with marked constriction of the cerebral vessels (*scotomata, hemianopia, photophobia,* and *unilateral paresthesia*). The second phase is accompanied by marked arterial pulsations (*throbbing* and *pain*). The third phase shows arterial rigidity with continued pulsations. The symptoms of this phase are excruciating *head pain, nausea, vomiting,* and *xerostomia.* Since ergotamine acts as a vasoconstrictor to the cerebral vessels and diminishes the pulsations, it is clear that best results will be achieved by its use in the prodromal or first phase. Here it may act prophylactically in preventing pulsations of great amplitude and vasodilatation which characterize the second phase concomitant with pain.

Ostfeld (1960) suggests the possibility of the migraine syndrome being caused by the action of serotonin. He lists the features of migraine which are compatible with the effect of serotonin. These are: local edema and hyperemia, local lowering of deep pain thresholds, effectiveness of ergotamine (each contains an indole nucleus), flushing and/or mottled cyanosis and occasional diarrhea and urinary frequency. The 2 features not compatible with the serotonin effect are arterial and venous dilatation. He was able to induce the migraine syndrome in 4 of 13 migrainous patients by the administration of 0.2 to 2 mg. of serotonin intravenously. The attack was indistinguishable from former migraine attacks in which exogenous serotonin was not the precipitating cause. In those patients, in which serotonin elicited a migraine attack, the administration of brominated lysergic acid, 0.25 to 0.5 mg. daily, provided adequate prophylaxis. In the other patients it was ineffective. Ostfeld suggests that in a segment of migrainous patients it is possible that the effect of serotonin is definitely involved. Germane to this concept of the etiology of migraine, Sicuteri *et al.* (1961) observed an increase in urinary 5-hydroxyindolacetic acid excretion in 15 patients during attacks of migraine headache. This is perhaps indicative of some concomitant change in serotonin metabolism. Further supportive evidence is found in the studies of Sicuteri *et al.* (1961) who used the butylamide of *l*-methyllysergic acid in 18 migrainous patients with notable improvement—decrease in number of attacks or complete freedom from further attacks as the result of the treatment with this anti-serotonin agent. This anti-serotonin agent is now available for prophylaxis in migrainous patients under the name of *methysergide* or *Sansert*. Thus, this refreshing and rewarding approach to the etiology of migraine has not only elucidated the origin of the disorder, but produced an effective drug for prophylaxis.

The effectiveness of ergotamine in migraine is greatest in the early stages of the attack. At this time 0.25 ml. (0.13 mg.) of Gynergen solution is given intramuscularly. This dose may be repeated if necessary, giving 2 ml. (1 mg.) in the course of a day. The drug is claimed to be effective in 70 to 98 per cent of the cases. The effective dose in patients in which the drug affords relief is from 0.1 to 0.25 ml. The smallest possible effective dose is recommended owing to the possibility of the development of symptoms of *ergotism*, page 749. The intravenous dose of the drug is 0.25 mg.; 0.5 mg. may be given in 24 hours and further up to 2 mg. per week (Moench, 1951). The effect is more prompt intravenously.

Orally the drug appears to be less effective. One tablet (1 mg.) is given every hour up to 5 tablets. As a rule not more than 10 tablets should be taken in 1 week. If nausea and vomiting preclude the giving of ergotamine orally, the drug may be administered sublingually. The absorption is prompt from beneath the tongue and the sublingual dose is about half the oral dose.

The continual ingestion of ergotamine as a prophylactic in migraine is inadvisable. The possibility of ergotism is always present. Although its occurrence is rare, the seriousness of its nature cautions one against too frequent medication with ergotamine. When used in the migrainous attack, or just prior to the attack repeatedly, tolerance or increased susceptibility does not usually appear to develop. Friedman and von Storch (1955) encountered an occasional patient who took ergotamine daily for several years and developed more attacks of headache than had occurred prior to medication. They feel that this phenomenon is related to the development of tolerance on the part of the patient to ergotamine. In these cases ergotamine withdrawal headaches appear to develop. The problem of habituation to ergotamine has not been thoroughly investigated.

Ergotamine alone or with caffeine remains the drug of choice in migraine. Success of this therapy in one attack in any patient generally bespeaks the repeated successful use of the drug in subsequent attacks.

**Ergotamine tartrate and caffeine.** Other drugs are often given with ergotamine in the treatment of migraine. Caffeine appears to be valuable. The preparation available is *Cafergot*, which contains 1 mg. of ergotamine tartrate and 100 mg. of caffeine in each tablet. Horton *et al.* (1948) found the combination effective in many patients who had not had success with ergotamine alone. There are often fewer side effects, and the dosage schedule of ergotamine may be reduced when Cafergot is used. Friedman (1950) suggests that the synergistic action of caffeine depends upon its contributing further to the constriction of the cerebral vessels and also to its psychic stimulating action.

This combination therapy is also available in the form of rectal suppositories. The advantage of this dosage form is prompt absorption. The action is almost as prompt as that from the parenteral use of ergotamine. In addition, in patients where vomiting precludes oral therapy, the suppository is indicated. Literature surveys indicate excellent results with about half of the patients using the suppositories, good relief in about 25 per cent, and inadequate control of the pain in the remainder.

The Cafergot suppository contains 2 mg. of ergotamine tartrate and 100 mg. of caffeine. One rectal suppository is inserted at the onset of the attack. If relief is not afforded and no side effects experienced another may be inserted. In some patients ½ or even ¼ of a suppository may suffice to afford relief. The minimal effective dose is recommended.

Suppositories containing 2 mg. of ergotamine, 100 mg. of caffeine, 0.25 mg. of Bellafoline (combined belladonna alkaloids), and 60 mg. of phenobarbital sodium are available under the name of "*Cafergot-P.B.*" These provide cholinergic blocking and sedation in addition to the ergotamine-caffeine vascular activity.

Another very useful combination with ergotamine tartrate is available under the name of *Wigraine.* Each tablet contains ergotamine tartrate, 1 mg.; caffeine, 100 mg.; belladonna alkaloids, 0.1 mg.; and 130 mg. of acetophenetidin. Brazil and Friedman (1957) found marked reduction of the temporal artery pulsations within 10 to 15 minutes after the ingestion of 2 Wigraine tablets, with accompanying relief of pain in their patients.

Friedman (1957) recommends the use of chlorpromazine because of its anti-emetic and sedative action in migraine headache. It is especially valuable if the attacks are accompanied by nausea. It is usually administered in the beginning of the attack. Chlorpromazine is not a substitute for ergotamine and its combinations but is considered as adjunct therapy.

**Ergonovine.** Ergonovine maleate, the principal alkaloid of ergot used for obstetrical purposes, page 750, has been used with a limited degree of success in the treatment of migraine. It is sometimes successful in cases in which ergotamine fails. The dose of the drug orally is 0.2 mg. There are less side effects from ergonovine than from ergotamine. Therefore there are those who contend that its use should be tried before ergotamine. Lennox (1938) found oral ergonovine more effective than oral ergotamine in migraine. Ergonovine, however, is a more powerful oxytocic than ergotamine and therefore should be avoided in pregnancy. Most patients do not suffer with migraine during pregnancy (Moench, 1951).

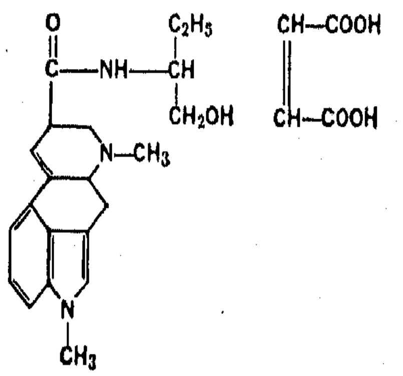
**Dihydroergotamine (D.H.E.-45).** Dihydroergotamine is the methane-sulfonate of hydrogenated ergotamine. Similar to ergotamine, it is an adrenergic blocking agent. Its toxicity, however, is about ½ that of ergotamine. Dihydroergotamine elicits no uterine contractions as does ergotamine. Besides, it is far less potent as a vasoconstrictor.

This drug has been repeatedly tried in cases of migraine and compared with ergotamine. Horton *et al.* (1945) found the 2 drugs equally efficacious in aborting acute attacks of migraine. When the 2 drugs were compared during alternate acute attacks of headache, 92 per cent were greatly relieved by Dihydroergotamine, and 77 per cent found ergotamine efficacious. The incidence of toxic symptoms with Dihydroergotamine was 4.5 per cent, far less than with ergotamine Hartman (1945) found the 2 drugs equally efficacious. When ergotamine failed to afford relief, as a rule, Dihydroergotamine was also ineffective. However, of Hartman's series of patients, many more suffered gastrointestinal distress from ergotamine than with Dihydroergotamine. In these cases Dihydroergotamine produced no demonstrable effects on pulse rate, blood pressure, pulsations of radial, dorsalis pedis, and posterior tibial arteries. There were no changes in the temperature or color of the extremities.

The dose of Dihydroergotamine is 1 mg. intramuscularly. It may be repeated in 1 to 2 hours. It has also been given subcutaneously and intravenously. The drug appears to offer a definite advance in migraine therapy. It is unfortunate that neither ergotamine nor Dihydroergotamine prevents the recurrence of the attacks. Of the ergot alkaloids useful in the treatment of migraine, owing to a definite lesser incidence of untoward side effects, Dihydroergotamine appears to be the drug of choice. However, owing to the necessity of parenteral administration, Dihydroergotamine is usually reserved for those patients who manifest untoward side effects with ergotamine tartrate, Cafergot or Wigraine.

Unfortunately, ergotamine and its preparations do not provide prophylaxis against repeated attacks of migraine. Psychotherapy is especially useful in determining which life situations precipitate an attack and advising the patient to avoid these. Other measures such as adequate relaxation and sleep, and adjustment of any other physiologic abnormality, are often helpful in reducing the number and severity of the attacks. The possibility of the attack's being precipitated by a substance to which the patient is allergic must also be considered. Added to the psychotherapy and available pharmacotherapy previously discussed is the comparatively new serotonin antagonist "methysergide" for prophylaxis.

**Methysergide, Sansert.** Methysergide is the maleate of *l*-methyl lysergic acid butanolamide as shown in the formula:



Methylsergide
Sansert

The compound occurs as white to pale reddish yellow crystals that are sparingly soluble in water.

**Pharmacologic response to methysergide.** In the rat the acute $LD_{50}$ of the compound is 125 mg./kg. I.V., and 2100 mg./kg. orally. Specific organ toxicity was not encountered in the rat or dog when the compound was administered at several dosage levels from 17 to 50 weeks.

The compound evokes marked antagonistic action to the edema provoking action of serotonin on various organs. Methysergide protects against the bronchospasm produced in guinea pigs by serotonin aerosol. In addition 10 μg./kg. of methysergide completely blocked the pressor response evoked in a dog by 30 μg./kg. I.V. of serotonin. Many other experiments demonstrated that methysergide is a specific antagonist to serotonin and also inhibits the release of histamine.

**Clinical use of methysergide.** Based upon the concept that migraine headache is associated with some defect in the storage, release, or metabolism of serotonin, methysergide was introduced as a drug to provide prophylaxis against the attack. It will be recalled that ergotamine, like methysergide, is a lysergic acid derivative, but is not valuable in migraine prophylaxis.

Numerous studies have confirmed the value of the drug in migraine prophylaxis and also in "cluster headaches" induced by histamine release. Data indicate that the drug affords relief in about 70 per cent of the cases of migraine headache uncomplicated by tension or psychogenic components by reducing the number of attacks, their severity, or producing their complete disappearance. For example, Friedman and Elkind (1963) used methysergide as a prophylactic treatment for 2½ years in 421 patients with vascular headaches of the migraine type. In all patients treated, whether for 2 months or longer than 22 months, a 64 per cent improvement was noted. Side effects usually occurred early in the treatment; they were frequent but usually mild. Other clinical studies parallel this one and indicate that prophylaxis can be expected in about ⅔ of a series of migrainous patients.

Pregnancy, peripheral vascular disease, severe hypertension, advanced coronary artery disease, a tendency toward thromboembolic disorders, and renal disease are considered contraindications to the treatment. Methysergide must be used cautiously in peptic ulcer.

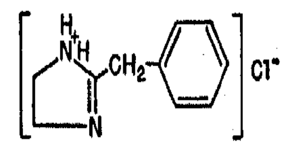
The side effects most frequently encountered are *nausea*, *heartburn* and *vomiting*. These effects are often obviated by giving the drugs with meals. Lightheadedness and dizziness have occasionally been reported.

The dose of methysergide must be most carefully adjusted to the needs of the patient. The average initial dose is 2 to 4 tablets (2 mg. each) daily with meals. The dose is gradually reduced to 1 tablet daily dependent upon the success of the prophylaxis and the freedom from side effects. The introduction of methysergide into medicine for prophylaxis in vascular headache represents a distinct advance in therapy. In addition, it has provided a provisional concept of the etiology of the syndrome. It is of more than passing interest that in most series of patients studied about ⅓ fail to experience relief. One wonders whether or not in this segment of the patients, serotonin is not implicated in the origin of the migraine.

## IMIDAZOLINE DERIVATIVES

Hartmann and Isler (1939) were the first to study the pharmacology of a large series of 2-substituted imidazoline derivatives. In this series they observed that 2-benzyl-2-imidazoline was the most active vasodepressor agent. They compared the action of these compounds with that of histamine, probably because of the common imidazole nucleus. They did not demonstrate the adrenergic blocking action of these compounds. The most potent compound of this series, 2-benzyl-2-imidazoline, called Priscol, now Priscoline (tolazoline), was later demonstrated to exhibit marked adrenergic blocking properties and was destined to become a useful therapeutic agent.

**Tolazoline Hydrochloride, U.S.P. (Priscoline Hydrochloride).** Tolazoline hydrochloride occurs in a white crystalline powder which is soluble in water. The structure is shown in the accompanying formula.



Tolazoline Hydrochloride, U.S.P.
Priscoline Hydrochloride
(2-benzyl-2-imidazoline hydrochloride)

There are 2 facets of the chemical structure of tolazoline which are of special significance. There is a phenyl group with an alkyl side chain which resembles the molecule of epinephrine. Also the molecule contains a histamine-like component, namely, the imidazoline nucleus. Like histamine, tolazoline produces dilatation by direct action on the walls of the arterioles and capillaries. Its action is more prolonged than that of histamine and not fraught with so many untoward side effects. Presumably that segment of the molecule which resembles the structure of epinephrine is responsible for its blocking of the action of epinephrine and norepinephrine.

**Pharmacologic responses to tolazoline.** Tolazoline has been the subject of many pharmacologic investigations designed to shed light on its mechanism of action. Meier and Müller (1941) perfused the vessels of a rabbit's isolated lower extremity. They maintained a constant tonus by the addition of epinephrine to the perfusion fluid. The addition of tolazoline produced vasodilatation within 3 minutes in the presence of epinephrine. Atropine which inhibits the vasodilating action of acetylcholine did not antagonize the action of tolazoline. They concluded that tolazoline elicited its response by blocking the effect of epinephrine in the receptor cells.

Yonkman and his associates (1945) studied tolazoline in urethanized cats. They found:

1. "Tolazoline, 15 to 20 mg., had no effect on salivation or the pupil.
2. Tolazoline, 1 mg., produced a marked, sudden retraction of the nictitating membrane and an acute hypotension enduring for approximately 30 minutes.
3. Tolazoline, 15 to 20 mg., produced a marked and sudden lowering of blood pressure (up to 50 per cent) which endured for a period of 3 hours or more, during which pulse and respiration seemed unaffected.
4. The effect of epinephrine, 10 μg., was reversed from the usual hypertensive to a hypotensive phase. This effect prevailed after 15 to 20 mg. of tolazoline for approximately 3 hours, after which a gradual return to normal epinephrine responses ensued. During recovery biphasic reactions prevailed in which initial hypertension was followed by hypotension. With each successive dose of epinephrine the hypertensive phase became more prominent while the hypotensive phase became less marked with return to normotensive levels.
5. Salivation and pupillary responses to epinephrine were not affected by tolazoline, 15 mg.

   Thus, although tolazoline, 15 mg., was adrenolytic in relation to blood pressure, it was not adrenolytic or sympatholytic in respect to the cervical sympathetic functions studied."

Thus it was demonstrated by the experiments cited and also by other studies that tolazoline was capable of effectively establishing an adrenergic blockade. This is especially marked with regard to the vasopressor action of epinephrine. Toxicity studies of the compound in various laboratory animals indicated its availability in man. The liver was shown to be the site of detoxification. The compound enjoys use clinically as an adrenergic blocking agent. Its special field of usefulness appears to be in *peripheral vascular disease.*

**The therapeutic use of tolazoline.**

1. The principal use of tolazoline is in the treatment of *peripheral vascular disease.* The treatment is directed toward the dilatation of the peripheral vessels by the adrenergic blockade of the drug; this affords a restoration of the patency and normal caliber of the involved blood vessels. Accordingly, tolazoline has found application in the treatment of *Buerger's disease*, *Raynaud's disease*,

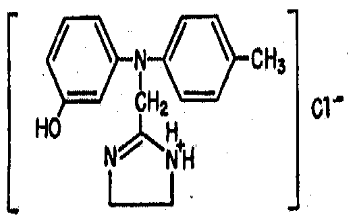
*thrombophlebitis*, *frostbite*, and *causalgic states*. In these conditions there are many favorable clinical reports and the drug has warranted a definite place in the physician's armamentarium.

2. Other uses of tolazoline. Tolazoline has been used with limited success in other conditions involving vascular spasm such as cerebral vascular spasm and primary cochlear ganglion-cell ischemia.

**Dosage and side effects of tolazoline.** Tolazoline is available by intravenous and oral administration. Its dosage by either route is 25 to 75 mg. 1 to 4 times daily. The oral administration of the 25-mg. tablet is seldom accompanied by any untoward effects. The most common experience is that of *cutisanserina*. Formication, flushing, and occasionally tachycardia are encountered. The intravenous dose may cause a sensation of warmth on the skin of the face and arms. Tolazoline may cause the activation of dormant peptic ulcers through increased acid secretion. Protection with antacid therapy is desirable in these cases.

**Fate of tolazoline.** Brodie *et al.* (1952) studied the fate of tolazoline in the tissues of man and the dog. When administered to either species it has a half-life of about 2 hours and is excreted essentially unchanged in the urine. The renal excretion of tolazoline is accomplished by a tubular secretory transport mechanism in addition to glomerular filtration.

**Phentolamine Hydrochloride, U.S.P. (Regitine Hydrochloride).** Phentolamine hydrochloride is another imidazoline derivative which produces adrenergic blocking. Its structure is shown in the formula.



Phentolamine Hydrochloride, U.S.P.
Regitine Hydrochloride
[2-(N′-*p*-Tolyl-N′-*m*-hydroxyphenylamino-methyl)-imidazoline hydrochloride]

Phentolamine is available in a lyophilized form for intravenous or intramuscular injection in the form of its methanesulfonate salt. For oral administration the hydrochloride of the base is used. Phentolamine hydrochloride occurs as a white or slightly grayish crystalline powder. It is soluble in water to the extent of 2 per cent.

Phentolamine is an effective adrenergic blocking agent, as shown by various pharmacologic procedures. It blocks the hypertensive action of injected epinephrine or norepinephrine. In blocking the vasoconstrictor effect of epinephrine, Roberts *et al.* (1952) found phentolamine to be effective in about ⅙ the dose of tolazoline. Yonkman *et al.* (1952) observed that 0.3 mg./kg. afforded complete protection in mice against an otherwise lethal dose of epinephrine. Trapold *et al.* (1950) induced sympatho-adrenal discharge in fully atropinized dogs by the injection of carbaminoylcholine. A typical diphasic rise in blood pressure resulted. Phentolamine caused a reversal of this response with a fall in blood pressure. This indicates that phentolamine produces reversal of the blood pressure rise owing to sympatho-adrenal discharge as well as that elicited by the injection of epinephrine. Chronic and acute toxicity studies in different species demonstrated that phentolamine was available for human use.

**Therapeutic uses of phentolamine.** Phentolamine is useful in those conditions in which tolazoline, page 569, is valuable. The principal use of phentolamine is in the diagnosis of pheochromocytoma. For this latter purpose the drug appears to be more positive than Benodaine and to produce less untoward side reactions. For diagnosis of pheochromocytoma, 5 mg. of phentolamine is used intravenously or intramuscularly.

Pheochromocytoma is a far more common disease than it was formerly considered to be. In the diagnosis of the disease, DeCourcy (1953) states, "The specificity, accuracy, convenience, and safety of phentolamine has established it as the testing agent of choice for routine use in screening all hypertensive patients." The test is almost devoid of side effects and has become an office procedure. Phentolamine does not elicit alarming increases in blood pressure as does Benodaine occasionally in essential hypertension. Following the administration of a diagnostic dose of phentolamine a typical positive response in a patient with pheochromocytoma is shown by a prompt fall in blood pressure of more than 35 mm. systolic and 25 mm. diastolic. The drug should also be available during the surgical procedure, which may evoke the release of the adrenergic hormones, causing an alarmingly high blood pressure.

Confirmatory evidence of pheochromocytoma may be produced by the determination of the urinary excretion of catecholamines. In normal individuals the epinephrine-norepinephrine excretion in a 24-hour urine specimen is 20 to 40 μg. In pheochromocytoma this value may increase 10- to 50-fold (Engel and von Euler, 1950).

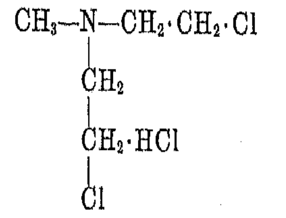
Nourok *et al.* (1963) reported an interesting case of phentolamine-resistant pheochromocytoma in a 16-year old girl. During the operation her blood pressure was maintained by intravenous infusion of sodium nitroprusside. No serious side effects were observed. This is an interesting and useful observation and may prove of great value in phentolamine-resistant cases of pheochromocytoma.

In the treatment of peripheral vascular disease, phentolamine is usually administered orally in 50-mg. tablets 4 to 6 times a day. Untoward side effects which have been encountered are *tachycardia*, *orthostatic hypotension*, *nasal stuffiness* and *gastrointestinal distress*. Withdrawal of the drug or diminished dosage for a period usually is sufficient to overcome these side effects.

The adrenergic blocking action of phentolamine is shown in figure 35-3 by Yonkman *et al.* (1952).

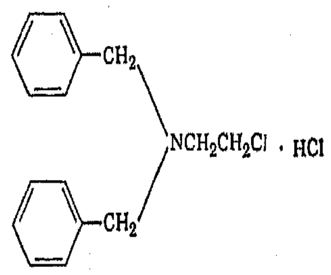
### β-Haloalkylamines

**N,N-dibenzyl-β-chloroethylamine (Dibenamine).** One of the most interesting adrenergic blocking agents is Dibenamine. Dibenamine chemically may be looked upon as a derivative of nitrogen mustard, page 911. The structures are shown in the accompanying formulas.



$$\begin{array}{l} CH_3\text{—}N\text{—}CH_2\cdot CH_2\cdot Cl \\ \quad\quad\;\; | \\ \quad\quad\; CH_2 \\ \quad\quad\;\; | \\ \quad\quad\; CH_2\cdot HCl \\ \quad\quad\;\; | \\ \quad\quad\; Cl \end{array}$$

Nitrogen Mustard
(methyl-bis-β-chloroethylamine
hydrochloride)



Dibenamine
(N,N-dibenzyl-β-chloroethylamine
hydrochloride)

Dibenamine has been studied pharmacologically and clinically by Nickerson and Goodman (1945, 1947). The free base is an oily liquid, but the hydrochloride is a white crystalline compound

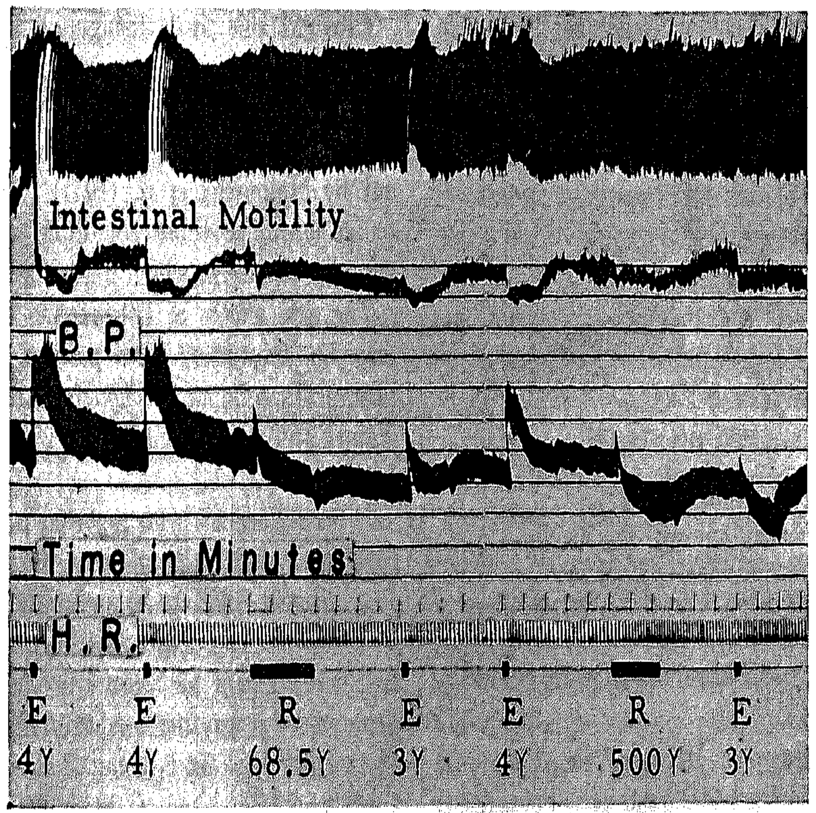


FIG. 35-3. Adrenergic blockade by phentolamine. Carotid artery blood pressure, *B. P.*; heart rate, *H.R.*, 28 beats/stroke. Drugs: Epinephrine, *E*; Regitine, *R*; (phentolamine). Doses/kg., (*Yonkman et al., 1952*.)

slightly soluble in water. Its solubility is increased by the addition of a small quantity of hydrochloric acid.

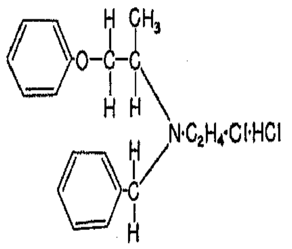
Nickerson and Goodman (1947) exhaustively studied the pharmacologic responses to Dibenamine in laboratory animals. The compound produces an epinephrine reversal in blood pressure, presenting a response similar to ergotamine, page 563. The compound was studied on various structures innervated by adrenergic fibers and was found to block effectively the effects of liberated norepinephrine and epinephrine.

Dibenamine produces local tissue damage and also causes central nervous system stimulation. Rapid intravenous injection will elicit coordinated clonic convulsions. When the compound is injected slowly these may be avoided. Orally the effects of Dibenamine are capricious.

Many analogs and homologs of Dibenamine have been studied. None of these appears to be superior to Dibenamine for clinical use.

The intravenous dose of Dibenamine is 4 to 6 mg./kg. The activity peak is reached within 24 hours and in some individuals its adrenergic blocking effects last several days. Although Dibenamine is an effective laboratory tool as an adrenergic blocking agent, clinically its action is capricious and fraught with too many side effects.

**Dibenzyline (Phenoxybenzamine).** One of the congeners of Dibenamine, N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride, appears to produce a more powerful adrenergic blockade than Dibenamine. Its structure is shown in the following formula:



Dibenzyline
(N-phenoxyisopropyl-N-benzyl-β-chlorethylamine hydrochloride)

Dibenzyline occurs in colorless crystals which are insoluble in water, but soluble in warm propylene glycol.

**Pharmacology of Dibenzyline.** The intravenous injection of 1 to 2.5 mg. of Dibenzyline in cats was found to produce total adrenergic blockade as shown by the reversal of the pressor effect of epinephrine. It was absorbed through the gut when given orally and produced blockade for 24 to 48 hours. As a typical adrenergic blocking agent it was found not to block the inhibitory adrenergic responses, such as the relaxation of smooth muscle. Acute and chronic toxicity studies in a variety of laboratory animals indicated the availability of this agent for clinical trial.

Cotton *et al.* (1957) studied the capacity of the commonly used adrenergic blocking agents to inhibit the increases in cardiac contractile force produced by norepinephrine, epinephrine and isoproterenol in dogs with intact circulatory systems. Of the five agents studied only Dibenzyline and phentolamine blocked completely the cardiac actions of the amines. Ilidar was from 50 to 75 per cent effective. It would have been of interest to have included tolazoline in the group of adrenergic blocking agents.

Brodie *et al.* (1954) showed that Dibenzyline, similar to Dibenamine, is dealkylated in the body of the dog to produce the corresponding amine. The amine minus the halogen chlorine, exhibits only weak adrenergic blocking activity. Although this is the major pathway of metabolism of Dibenzyline, these investigators suggest the possibility of other modes of metabolism.

It appears that the adrenergic blockade produced by Dibenzyline is complete and longer in duration than that elicited by the other commonly used adrenergic blocking agents.

**Clinical use and dosage of Dibenzyline.** There are many clinical reports on the successful use of Dibenzyline as an adrenergic blocking agent. Pioneer work with the drug was carried out by Haimovici *et al.* (1951). The drug was found useful in those conditions of peripheral vascular disease in which tolazoline is valuable.

The side effects of Dibenzyline therapy that may be encountered are *postural hypotension, tachycardia, mild nasal congestion,* and *drowsiness. Nausea* and *vomiting* may occur with high dosage levels.

Dibenzyline has been reported by the Southeast Scotland Faculty of the College of General Practitioners (1957) to be useful in the treatment of *chilblains.* The dose was 10 mg. daily for the first week, and if no untoward effects were encountered this was increased to 10 mg. twice daily the second week and 10 mg. 3 times a day the third week. Complete remission was observed in 24 of 28 patients. Distressing side effects made it necessary to discontinue the use of Dibenyzline in 9 of 59 patients. The commonly encountered side effects of this drug are mentioned in the foregoing paragraph.

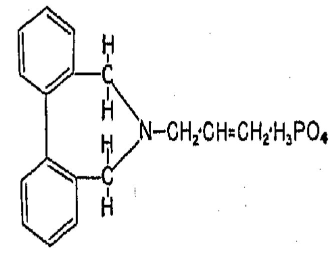
Dibenzyline is available in 10-mg. capsules. In peripheral vascular disease the dose may vary from 20 to 60 mg. daily. It is always advisable to start therapy with low dosage levels until adrenergic blockage is established.

Moser (1958) comprehensively reviewed the therapeutic status of Dibenzyline. The evidence is clear that it is a potent adrenergic blocking agent. He asserts, "Its usefulness in clinical medicine is limited by side effects, the development of tolerance to drug effect and occasionally irregular action when administered orally." Moser listed the conditions in which Dibenzyline had been found most effective as Raynaud's disease and associated conditions, post-frostbite syndrome. Buerger's disease, and hyperhidrosis.

### Dibenzazepine Derivatives

Wenner in 1951 described the preparation of a new class of adrenergic blocking agents, namely, the dibenzazepine derivatives. The pharmacology of the series of compounds was studied by Randall and Smith (1951) and Moore *et al.* (1952). Of this series Ilidar appeared to offer most promise for clinical trial.

**Ilidar, Azapetine.** The adrenergic blocking agent Ilidar is shown in the following formula:



Ilidar
Azapetine
(6-allyl-6,7-dihydro-5H-dibenz [c, e] azepine phosphate)

Ilidar phosphate is a colorless crystalline powder eliciting a bitter taste. It is soluble to 2.5 per cent in water at room temperature.

**Pharmacology of Ilidar.** Randall and Smith (1951) found Ilidar effective in producing adrenergic blockade as shown by a reversal of the pressor response of epinephrine and norepinephrine. It blocked the carotid sinus reflex in doses that were higher than those required for the epinephrine reversal effect. Ilidar protected the myocardium of the dog against fibrillation produced by chloroform and epinephrine, and elicited direct vasodilating activity.

Ilidar appears, from its pharmacologic studies, to be a potent but short-acting adrenergic blocking agent. Upon oral administration Ilidar causes a prolonged depressor action. It does not block the inhibitory actions of epinephrine on smooth muscle. Ilidar exhibits a relatively low toxicity.

**Clinical use and dosage of Ilidar.** Green and DuBose (1954) studied Ilidar clinically in peripheral vascular disease and similar conditions. They found Ilidar effective in the treatment of patients with predominantly vasospastic disorders. Subjective improvement occurred in 5 of 8 patients with Buerger's disease and in ⅓ of 29 patients having arteriosclerosis obliterans.

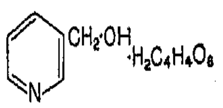
Ilidar was well tolerated by most patients (74 out of 86). The most common side effects were *vertigo, nausea, weakness, syncope,* and *drowsiness. Drug fever* and *severe nausea* were encountered in 1 patient. Their opinion is that the side effects were mild compared to those encountered with the other adrenergic blocking agents.

Most of these patients were given 2 or 3 25-mg. tablets of Ilidar daily. In more severe cases the dose was elevated to 300 to 400 mg. daily. It is of special interest that Johnson *et al.* (1953) studied the relative adrenergic blocking capacities of tolazoline, phentolamine, and Ilidar in the vessels of the dog's leg. The ratio of the doses of the 3 drugs was found to be the same for epinephrine reversal, blocking of norepinephrine constriction, and the blocking of epinephrine dilatation in the vessels of skeletal muscle. The duration of response increased with the dose of each blocking agent, but the degree of response was constant.

Green *et al.* (1954) studied the effectiveness of four adrenergic blocking agents by measurement of the blood flow in the hind leg of the dog. On an equal weight basis the following order of effectiveness was determined: Dibenzyline > phentolamine > Ilidar > tolazoline. Dibenzyline blocked all responses at the lowest doses of any of the four drugs. They further observed that the primary dilator responses (reversal) to the adrenergic hormones were evoked by these agents in the following order of decreasing effectiveness: Dibenzyline > Ilidar > phentolamine > tolazoline. This is suggestive that Dibenzyline and Ilidar are relatively more effective in their blockade of the alpha adrenergic receptor as compared to the beta receptors than phentolamine or tolazoline.

Of the three adrenergic blocking agents currently used in peripheral vascular disease, evidence appears to be unequivocal that Dibenzyline is more potent and longer-acting than tolazoline or Ilidar. Agarwal and Harvey (1956) presented evidence to show that the longer duration of action of Dibenzyline is due to a "firm chemical combination of the drug with a cellular receptor substance and not due to its storage in body fat."

**Roniacol (β-pyridyl-carbinol).** Roniacol is not an adrenergic blocking agent, but owing to the fact that its principal use is in the treatment of peripheral vascular disease it is discussed in this chapter. Roniacol is the tartrate of the alcohol obtained by the reduction of nicotinic acid, as shown in the accompanying formula.



Roniacol Tartrate
(Nicotinic Alcohol Tartrate)

Roniacol tartrate is a white, crystalline, stable salt which is freely soluble in water.

**Pharmacologic and therapeutic action of Roniacol.** The marked vasodilating action of nicotinic acid was observed by Spies *et al.* (1938). The dilating action of nicotinic acid is mainly in the capillary vessels. The response is prompt but of short duration. Many compounds analogous to nicotinic acid have been studied for their vasodilating effects. It has been revealed that to elicit the vasodilating effect of nicotinic acid the radical nicotinate must be present in the circulation at a sufficient level.

By the reduction of nicotinic acid to the corresponding alcohol one can provide the tissues with a continuing source of nicotinic acid. This results from the oxidation of the alcohol to the acid. The effect is thus prolonged. It is upon this principle that therapy with Roniacol depends.

When administered intravenously to dogs, Roniacol produces a definite rise in leg volume. This is accompanied by a fall in blood pressure of 20 to 30 mm., indicating peripheral vasodilatation. Recordings of pressure simultaneously from the peripheral end of the severed femoral artery and the carotid artery, upon the intravenous injection of Roniacol, showed a fall in peripheral arterial pressure but no change in the carotid blood pressure. This is indicative of increased blood flow to the leg. When administered to man orally the peripheral vasodilatation becomes manifest promptly by marked reddening of the nail-beds.

In various clinics Roniacol has been shown to be effective in the treatment of *Buerger's disease, Raynaud's disease, intermittent claudication, frostbite,* and *vascular spasm.* Murphy (1951) used Roniacol in 22 cases of peripheral arterial disease and obtained encouraging results in most instances. The side effects were minimal. Several patients complained of heartburn which disappeared with continued therapy. Richter *et al.* (1951) used Roniacol in 50 cases of arteriosclerosis obliterans and found improvement in 20 patients. They found Roniacol to be more effective as a peripheral vasodilator than other agents commonly employed. Texter *et al.* (1952) critically compared Roniacol, Priscoline, Pronestyl, and certain new adrenergic blocking agents in arteriosclerosis obliterans. They were favorably impressed by the results observed with Roniacol and Priscoline.

Fisher and Tebrock (1953) studied Roniacol over a 3½-year period in 218 patients. They used doses up to 1200 mg. daily with no toxic manifestations. They concluded that Roniacol was of definite value in the treatment of the intermittent claudication of peripheral arteriosclerosis and thromboangiitis obliterans. They found it to be of no value in Raynaud's disease.

Samuels and Tuchman (1955) made plethysmographic studies of the peripheral circulation following the administration of several vasodilators to patients with arteriosclerosis obliterans. Among these were Roniacol and Ilidar. Each produced definite increases in blood flow in the digits. They observed no quantitative difference.

Roniacol appears to have a definite place in the treatment of peripheral vascular disease. Some clinicians alternate between a course of Roniacol and tolazoline medication in the belief that better results are thus experienced by their patients. Roniacol in the form of its tartrate is available in 50-mg. tablets. The daily dosage is from 150 to 600 mg.

**Cyclandelate, Cyclospasmol.** Cyclospasmol is another type of drug used in the treatment of peripheral vascular disease. Chemically the compound is 3,3,5-trimethylcyclohexyl mandelate. Pharmacologic evidence indicates that Cyclospasmol is not an adrenergic blocking agent, nor does it act through the stimulation of the sympathetic dilator mechanism as does Arlidin, page 557. Its action appears to be mediated through a direct

musculotropic effect upon the smooth musculature of the arterioles.

**Clinical use of Cyclospasmol.** Cyclospasmol increases the digital blood flow and produces an elevation in skin temperature. The drug is indicated in the variants of peripheral vascular disease. Its relative efficacy in comparison to the other agents available for this purpose has not been adequately assessed. Side effects with Cyclospasmol include *tingling, flushing, dizziness, sweating, nausea,* and *headache.* These side effects occur in about ⅓ of the patients receiving daily doses of 800 mg. or more. The usual dose is 100 mg. 4 times daily. The comparative freedom from severe side effects warrants the trial of this drug in peripheral vascular disease, as adjunctive treatment to other drugs, or as the drug to be considered when other drugs fail or produce intolerable side effects. The European literature on the use of the drug is enthusiastic. That in America is fragmentary but in the main favorable (Gillhespy, 1956).

### OTHER ADRENERGIC BLOCKING AGENTS

**Benodaine Hydrochloride.** Benodaine hydrochloride is a dioxane derivative which is used expressly for the diagnosis of pheochromocytoma. The dose is 15 to 20 mg. intravenously. Its use is similar to that of phentolamine, but owing to its untoward side effects it has been largely replaced by phentolamine. For a more detailed description of Benodaine see 4th edition, page 778.

**Yohimbine.** Yohimbine is an alkaloid obtained from the bark of the West African tree *Yohimbeche.* Large intravenous doses of the alkaloid reverse the action of epinephrine as does ergotamine. Toxic doses of the alkaloid produce first stimulation of the central nervous system and then depression. The depression is marked in the medulla, and death is caused by respiratory paralysis. The drug also produces cardiotoxic effects. Yohimbine has been used unsuccessfully as an aphrodisiac in a 5-mg. dose. It dilates the vessels of the skin and mucous membranes, particularly of the sex organs. It apparently is worthless in the stimulation of libido.

It is evident that the adrenergic blocking action of the alkaloid is only one of the many powerful actions of the drug. Its pharmacologic syndrome is consequently complicated and fraught with toxic manifestations. Its use as a possible adrenergic blocking agent clinically is therefore precluded. It is of more than passing interest that the molecule of yohimbine contains a chemical nucleus similar to that of reserpine (page 498).

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# 36

# *Parasympathetic Division of the Autonomic Nervous System (Cholinergic Agents)*

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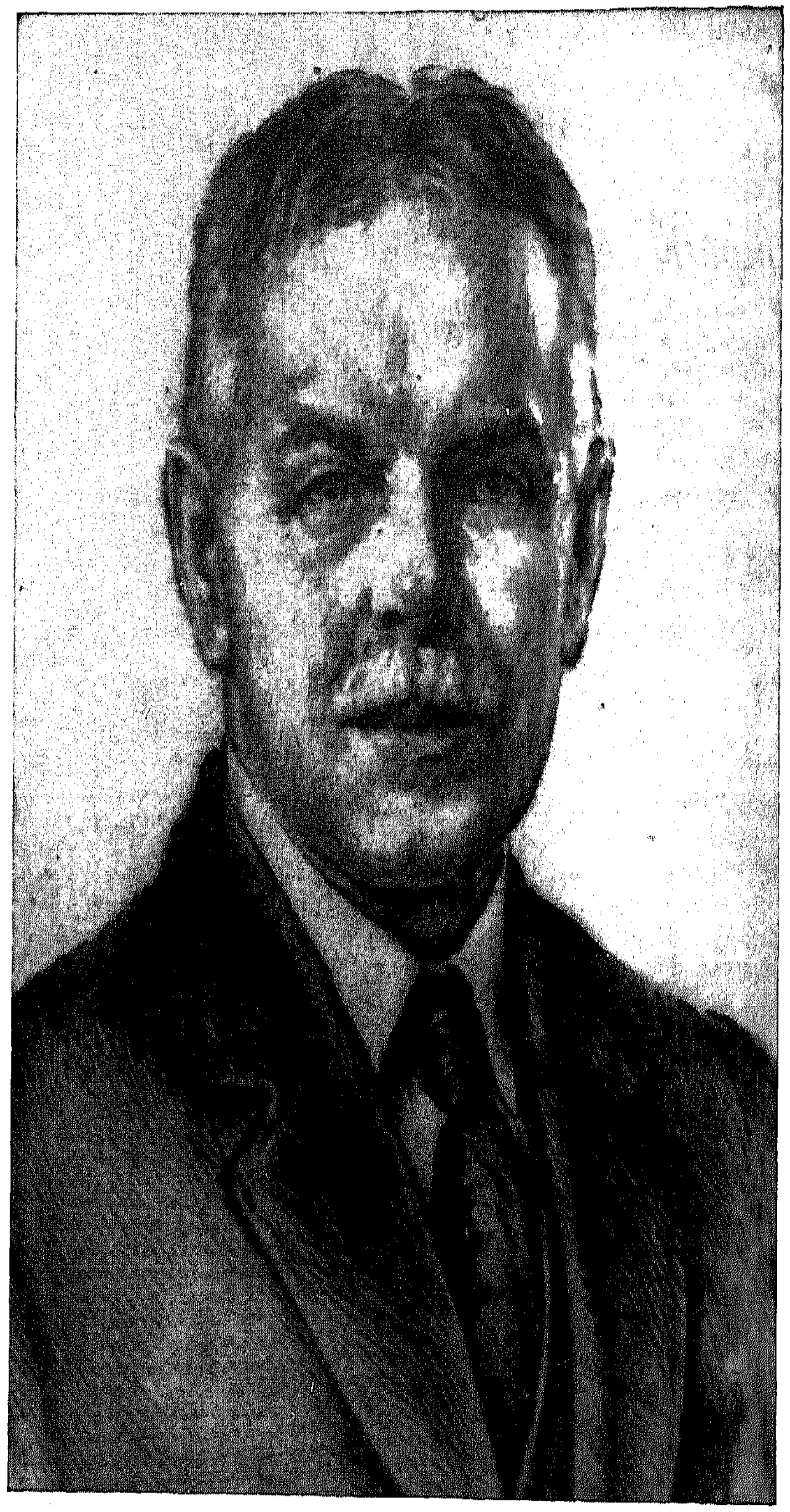
## Choline and Choline Esters

**Choline.** It has been stated previously that the activity of choline as a parasympathomimetic drug is increased several thousand times by esterification. Especially is this true by acetylating the compound, preparing the hormone of this division



REID HUNT

1870–1948

*Brilliant pharmacologic investigator who isolated acetylcholine from the adrenal medulla*

"I think it is safe to state that, as regards its effect upon circulation it (acetylcholine) is the most powerful substance known. It is one hundred thousand times more active than choline, and hundreds of times more active than nitroglycerin; it is a hundred times more active in causing a fall of blood pressure than is adrenalin in causing a rise."

of the autonomic nervous system, acetylcholine. Accordingly, in therapeutics choline is not used for its cholinergic action, but its more active esters are employed.

**Acetylcholine.** The principal responses elicited by acetylcholine have been discussed in the preceding chapters. Its use in therapeutics is very limited. The peripheral vasodilating action of acetylcholine is very marked but very short in duration. It is rapidly destroyed by cholinesterase. In addition, the peripheral vasodilatation produced by acetylcholine is accompanied by its action on the autonomic ganglia and on skeletal muscle.

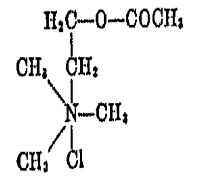
For the foregoing reasons pharmacologists have sought for choline esters that would:

1. Produce a longer vasodilatation;
2. Be devoid of the action on the autonomic ganglia;
3. Not produce stimulation of skeletal muscle.

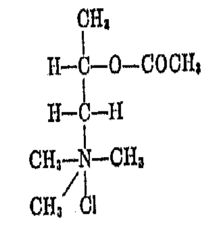
Hunt and Traveau (1911) and Hunt and Renshaw (1926) prepared and studied over 300 choline esters and related compounds. Not any of these esters is as active as acetylcholine.

Although Hunt and his associates prepared $\beta$-methylacetylcholine chloride many years ago, its value as a therapeutic agent was not established until Simonart (1932) and Starr *et al.* (1933) studied the substance in animals and man. The substance was first marketed under the name of "Mecholyl."

**Methacholine Chloride, N.F. (Mecholyl Chloride).** Methacholine chloride is a white crystalline powder. It is very deliquescent in the air. The powder is very soluble in water. The relation of methacholine chloride to acetylcholine chloride is shown in the accompanying formulas.



Acetylcholine Chloride



Methacholine Chloride
(mecholyl chloride)

The action of methacholine differs from that of acetylcholine principally in the fact that the former is devoid of the ganglionic and skeletal muscle actions of acetylcholine. It is acted upon only by specific cholinesterase and hence its action persists for a longer period. It is not so potent as acetylcholine and is active upon oral administration.

Methacholine bromide is also available. It is less hygroscopic than the chloride.

**Principal actions of methacholine.** Methacholine emulates the action of acetylcholine on the receptor cells of the cholinergic fibers. It stimulates the vagus and produces bradycardia. It stimulates the receptor cells of the cholinergic fibers of the sympathetics which dilatate the arterioles and produce a fall in blood pressure through peripheral vasodilatation and cardiac slowing. Methacholine stimulates the smooth musculature of the bronchi, intestines, bladder, and uterus owing to their cholinergic innervations.

Starr *et al.* (1933) studied the effects of methacholine extensively in man. They found that when administered to normal individuals in doses of 10 to 20 mg. subcutaneously the following symptoms ensued within 2 minutes: flushing of the face and neck, sweating, salivation, slight fall in blood pressure, increased depth of respiration, and an initial rise in pulse rate followed by a slower rate than before injection. The action usually extends over a 20-minute period.

The oral administration of methacholine 50, to 1000 mg., is followed by the same pharmacologic syndrome. The action comes on more slowly, lasts from ½ to 1 hour, and is less intense. Peristalsis is increased and some epigastric discomfort may be experienced.

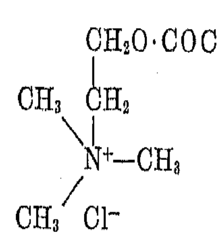
The drug should not be administered intravenously owing to the precipitous fall in blood pressure which is produced and the danger of bronchial spasm. The stimulating action of methacholine on the viscera innervated by cholinergic nerves is blocked by atropine.

**The therapeutic uses of methacholine.**

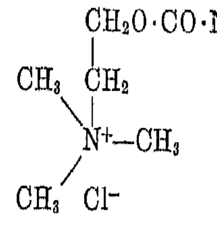
1. Methacholine is used successfully in the treatment of *paroxysmal tachycardia.* The vagal stimulating action of the drug causes a prompt cessation of the attack. Methacholine is indicated if the atrial tachycardia cannot be checked by carotid sinus pressure. The effective dosage subcutaneously is 10 to 40 mg. The attack is generally terminated within 2 to 5 minutes after injection. Starr (1935) states, "The degree to which the action, after subcutaneous injection, remains under control is surprising. By vigorous massage of the site of injection it can be intensified; by applying a tourniquet above this site it can be diminished, and at any time it can be brought to an end immediately by an injection of atropine."
2. Methacholine has been used successfully in *urinary bladder retention.* The cholinergic fibers of the parasympathetic nerves are

motor to the wall of the bladder and relaxant to the sphincter. In the atonic bladder following surgery, methacholine has been used with striking success. For this purpose 10 to 25 mg. subcutaneously is administered. In other conditions causing urinary retention such as *tabes dorsalis, spina bifida, infectious myelitis, multiple sclerosis, tumors,* and *injuries,* methacholine has been used to advantage.

**Carbachol, U.S.P. (Doryl, Carbaminoylcholine chloride).** Carbachol was synthesized by Kreitmair in 1932. It is the most potent choline ester. Carbachol is a white or faintly yellow crystalline powder. It is odorless and hygroscopic. One gram of the ester is soluble in about 1 ml. of water. The relationship of carbachol to acetylcholine is shown in the accompanying formulas.



Acetylcholine Chloride



Carbachol
(carbaminoylcholine chloride)

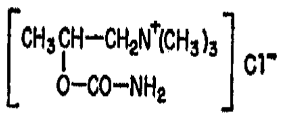
Carbachol is similar to acetylcholine in its pharmacologic responses. Unlike methacholine it stimulates the autonomic ganglia and stimulates the contraction of skeletal muscle. It is not hydrolyzed by cholinesterase.

**The therapeutic uses of carbachol.**

1. Carbachol is employed similarly to methacholine. It is a more potent and more dangerous drug. The evidence is not convincing to show that carbachol offers any advantage over methacholine in the conditions in which these choline esters are indicated.

   The oral dose of carbachol is 2 mg. and the subcutaneous dose is 0.25 mg.
2. Carbachol is used as a myotic in the treatment of glaucoma. The usual strength of the solution is 1.5 per cent. Caution should be exercised to avoid the *oral* or *parenteral* administration of this solution.

**Bethanechol Chloride, U.S.P. (Urecholine chloride).** This derivative of choline elicits pharmacologic effects similar to methacholine chloride. Chemically it is the urethane of $\beta$-methylcholine chloride, as shown in the accompanying formula.



$$\left[\begin{matrix}CH_3CH{-}CH_2\overset{+}{N}(CH_3)_3\\ |\\ O{-}CO{-}NH_2\end{matrix}\right]Cl^-$$

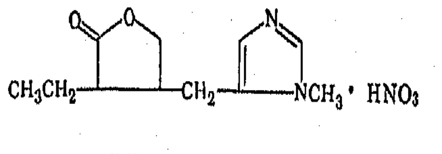
Bethanechol Chloride, U.S.P.
Urecholine Chloride

Bethanechol chloride occurs in hygroscopic crystals which emit a faint amine odor. The compound is soluble in less than its own weight of water.

The action of bethanechol is parasympathomimetic in character. It is not inactivated by cholinesterase. The compound has been found useful in the treatment of *gastric retention after vagotomy, postoperative urinary retention,* and in *postoperative abdominal retention.* Bethanechol has been used successfully in the treatment of such untoward side effects as urinary retention and constipation which often accompany the treatment of hypertension with ganglionic blocking agents.

Oral doses of 10 to 30 mg. 3 to 4 times daily generally suffice in conditions in which the drug is effective. It may be administered subcutaneously but not intravenously or intramuscularly. The subcutaneous dose is 2.5 to 5 mg.

**Pilocarpine Nitrate, U.S.P.** Pilocarpine nitrate is the nitric acid salt of an alkaloid obtained from the dried leaflets of *Pilocarpus jaborandi* or *Pilocarpus microphyllus.* It occurs in shining white crystals. It is not hygroscopic but is affected by light. One gram of the salt dissolves in about 4 ml. of water. The structure of pilocarpine nitrate is shown in the accompanying formula.



Pilocarpine Nitrate

The other common pilocarpine salts such as the sulfate and hydrochloride are hygroscopic. The nitrate is not hygroscopic and is therefore the salt of choice.

**Principal pharmacologic responses of pilocarpine.** Pilocarpine is a powerful stimulant to the organs innervated by cholinergic fibers. It mimics acetylcholine in its peripheral action. Its action is directly upon the effector cells in the viscera innervated by the cholinergic nerves. The action is not mediated through the inactivation of cholinesterase. In addition to its predominating peripheral action, pilocarpine also affects all autonomic ganglia by increasing the transmission of nerve impulses from the pre- to the postsynaptic fibers (Marrazzi, 1939).

By virtue of its cholinergic action pilocarpine *augments gastrointestinal activity.* It increases the flow of saliva, sweat, tears, mucus, and the gastric and pancreatic secretions. Pilocarpine causes a constriction of the pupil and concomitantly fixes the eye for near vision (spasm of accommodation).

The action of pilocarpine on the central nervous system is not marked. It is of interest, however, that the direct application of pilocarpine to the hypothalamic centers produces effects similar to its intravenous injection. This observation was made by Cushing (1931), who injected pilocarpine into the lateral ventricles of human subjects. They experienced a quickened pulse, sensation of heat, abundant salivation, and emesis. These results seem to indicate that the alkaloid acts locally on the parasympathetic centers in this area of the brain. The increase in pulse rate is likely due to a release of epinephrine caused by the drug.

**Diaphoretic action of pilocarpine.** Pilocarpine produces marked sweating. Agents which cause marked sweating are called *diaphoretics, sudorifics,* and *hidrotics.* Pilocarpine is the most powerful diaphoretic used in medical practice. When 5 mg. of the drug is injected subcutaneously, sweating begins almost immediately, and several liters of water may be lost through the skin from 1 injection. The dose may be repeated in ½ to 1 hour.

The diaphoretic effect of pilocarpine is directly upon the sweat glands. It also produces hyperemia in the areas where it is injected. This peripheral action of the drug is completely blocked by atropine and to a lesser extent by epinephrine.

This sudorific action of pilocarpine has been used to relieve edema in hydremic nephritis. The loss of water by sweating diminishes the load upon the impaired kidneys. The use of the drug in this capacity is fraught with many dangers, and its benefits are only temporary. The sudorific dose causes marked salivation and often nausea and vomiting. After preliminary acceleration, the pulse rate is markedly depressed. Sometimes a generalized depression of the individual may occur from the drug action. In addition, its action evoking bronchial constriction and increased mucus flow predisposes the individual to pulmonary edema. It appears that the untoward effects of the drug outweigh the temporary advantage gained by its use as a sudorific in edema.

**The action of pilocarpine on the gut.** Through the stimulation of vagal effector cells, pilocarpine increases peristaltic movements in the intestines. Quigley *et al.* (1934), in studying the effect of drugs on the movement of a soft bolus in the intestine, observed the action of pilocarpine to be inferior to other agents. The action in man is not always dependable when small doses are administered. Larger doses often produce severe tenesmus and intestinal discomfort. For this purpose neostigmine is a superior drug. It is more dependable, and its side effects are less.

**The action of pilocarpine on the eye.** Pilocarpine, when injected subcutaneously or instilled into the conjunctival sac, causes pupillary constriction (myosis) and a spasm of accommodation. The local pupillary action of pilocarpine is of importance clinically.

For this purpose, solutions of 0.5 to 4 per cent of the nitrate or hydrochloride of the alkaloid are used. They stimulate the effector cells innervated by the cholinergic fibers in the sphincter muscle of the iris and in the ciliary muscle. The former causes myosis, the latter a spasm of accommodation. The myosis begins in 10 to 15 minutes after instillation and persists for 15 to 24 hours. The spasm of accommodation occurs with the myosis but lasts only 2 to 3 hours. Each effect is blocked by atropine.

Clinically the ocular effects of pilocarpine are valuable in the treatment of glaucoma. The intraocular tension after an incipient increase is diminished. When the sphincter muscle of the iris is stimulated and the pupil constricted, a better drainage is established through the canal of

Schlemm in the angle formed by the iris and cornea. The smooth muscle of the iris is extended centrally away from the drainage canal. This increases the activity of the drainage canal and permits more readily the flow of the aqueous humor, thus diminishing intraocular tension.

After the refraction of the eyes for lenses, pilocarpine may be used to combat the cycloplegia produced by homatropine. Pilocarpine will also antagonize the mydriasis of homatropine by its myotic action.

**Pilocarpine in glaucoma.** It is estimated that of 800,000 cases of glaucoma in America in patients over 45 years old only about 10 per cent are caused by narrower angle or angle closure. The remaining 90 per cent are due to failure of the filtration process of the trabecular meshwork. The channels or spaces of Fontana found in lower species have probably, through phylogenetic change, been replaced by the delicate trabecular meshwork in higher animals and man. Since the fundamental defect lies in the filtration mechanism, widening the angle accomplishes little benefit. The aim of treatment is to reduce the fluid and improve the filtration mechanism.

For this purpose pilocarpine and not physostigmine is the myotic of choice. This drug, acting directly on the affector mechanism, similar to acetylcholine, stimulates the radial fibers of the ciliary muscle and affects a widening of the mesh filtration structure of the trabecular membrane. The application of epinephrine bitartrate ointment (2 per cent) twice daily reduces the amount of fluid by 15 to 25 per cent. This potent vasoconstrictor evokes ischemia in the ciliary processes, where the aqueous humor is formed, and inhibits the efficiency of the process by reduction of the blood supply. To enhance further the effectiveness of the treatment, pilocarpine may be used concomitantly to antagonize the mydriasis evoked by epinephrine, thus avoiding narrowing of the angle.

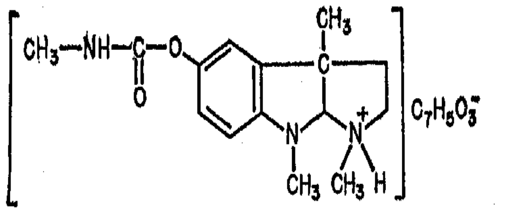
**The fate of pilocarpine in the body.** Pilocarpine is excreted in the urine in a free and conjugated form. The combined form of the alkaloid is decomposed by treatment with acidified alcohol.

**Toxicology.** Pilocarpine in toxic doses produces intense nausea, salivation, sweating, and vomiting. The heart rate is at first increased and then slowed by the drug. Severe gastrointestinal distress and diarrhea occur. Breathing becomes difficult owing to bronchial constriction and mucus flow. The pupils are constricted. The drug ultimately kills by paralyzing the heart or by the production of pulmonary edema.

Atropine is the best physiologic antidote for pilocarpine intoxication. Other measures of a supportive nature such as intravenous glucose and saline fluids by mouth or by vein to restore the water balance are indicated.

**The therapeutic uses of pilocarpine.** The therapeutic uses of pilocarpine are confined to its ocular action. It is used as a myotic in glaucoma and to combat the cycloplegia and mydriasis of atropine when the latter is used for refraction. The 2 per cent aqueous solution of the nitrate or hydrochloride of the alkaloid appears to be most generally employed.

**Physostigmine Salicylate, U.S.P. (Eserine salicylate).** Physostigmine salicylate is the salicylate of an alkaloid usually obtained from the dried ripe seed of *Physostigma venenosum.* It occurs as a white, or faintly yellow, shining crystalline powder. It becomes pink when exposed to the air. One gram requires 75 ml. of water for solution. The structure of physostigmine salicylate is shown in the accompanying formula.



Physostigmine Salicylate
(Eserine salicylate)

Formerly the sulfate of the alkaloid was also widely used. Each salt in aqueous solution becomes pink upon standing. The sulfate deteriorates more readily than the salicylate, therefore the salicylate is the salt which is preferred.

The seeds of the physostigma plant contain 0.15 per cent of physostigmine. The seed is called *ordeal bean* or *Calabar bean* by native Africans. Native medicine men administered a paste of ordeal beans to accused criminals. If the criminal vomited the paste and his life was spared, he was declared innocent. If emesis did not occur and the drug poisoned the individual, it was believed to be conclusive evidence of guilt.

**Principal pharmacologic responses to physostigmine.** Physostigmine is a powerful *stimulant to the organs innervated by cholinergic fibers.* It also causes the *contraction of skeletal muscle.* In these 2 responses it emulates the action of acetylcholine. Its action, however, differs from that of acetylcholine and pilocarpine inasmuch as its cholinergic and skeletal muscle responses depend mainly upon its inactivation of cholinesterase. It combines with cholinesterase, preventing the esterase from deacetylating acetylcholine. Thus it permits an action of acetylcholine uninterrupted by cholinesterase. The action of physostigmine with cholinesterase is reversible, and as the esterase is again liberated it hydrolyzes acetylcholine and nullifies its action.

By virtue of its cholinergic action physostigmine augments gastrointestinal activity. It causes pupillary constriction with a concomitant spasm of accommodation. Physostigmine antagonizes the action of curare on skeletal muscle. Its action on the central nervous system is not marked, but in larger doses it first stimulates, then depresses the central nervous axis. Physostigmine is not so active a stimulant to secretory mechanisms as is pilocarpine.

**The action of physostigmine on the intestine.** The smooth musculature of the intestines is stimulated by 2 mg. of physostigmine. It may be given by mouth, but the drug is more effective when injected subcutaneously. Peristalsis is initiated, and evacuation is produced by the drug. It has served successfully as a cathartic in postoperative intestinal atony. Neostigmine is now preferred to physostigmine.

**The action of physostigmine on the eye.** Physostigmine when injected or instilled into the conjunctival sac causes pupillary constriction and a spasm of the accommodation. The local pupillary action of physostigmine is of importance clinically.

For this purpose a 0.5 per cent physostigmine salicylate solution is used. The action of the drug on the pupil and ciliary muscle is prompt, occurring within 2 minutes after instillation and reaching a maximum within 1 to 2 hours. The effect persists for 12 to 36 hours.

The action of physostigmine in producing myosis and a spasm of accommodation depends upon its inactivation of cholinesterase. This permits an intensified action of acetylcholine on the effector cells of the sphincter muscle of the iris and on the effector cells of the ciliary muscle.

Clinically, the ocular effects of physostigmine are valuable in the treatment of glaucoma. The intra-ocular tension does not undergo an incipient increase as with pilocarpine, but the initial effect of physostigmine is one of reducing the tension. This is accomplished by the same physiologic mechanism as was discussed under pilocarpine, page 581.

Physostigmine is also used to antagonize the mydriasis and cycloplegia produced by atropine or homatropine after the refraction of the eye for lenses. It is also used alternately with homatropine to prevent the formation of adhesions between the iris and the cornea after certain ocular surgical procedures.

As it was stated previously, solutions of physostigmine salicylate become pink on standing. This is due to the formation of *eseroline.* This substance elicits responses similar to physostigmine, but it is more irritating to the conjunctiva.

**The response of skeletal muscle to physostigmine.** Physostigmine stimulates the contraction of skeletal muscle. This occurs in the isolated gastrocnemius muscle. Its irritability is increased by the peripheral action of the drug. The action is at the neuromuscular junction, at which site physostigmine inactivates cholinesterase. Miquel (1946) has shown that physostigmine acts directly on skeletal muscle, causing its contraction, in addition to its activity as an anticholinesterase agent. This was shown by the capacity of physostigmine to contract the isolated frog rectus abdominis muscle which had been previously treated with di-isopropyl fluorophosphate to inactivate the cholinesterase. The action of the drug on skeletal muscle is sometimes observed in human subjects when the solutions are instilled into the conjunctival sac. It may cause twitchings of the temporal or orbital muscles. These twitchings are observed in the muscles of the arms and legs when the drug is used in massive doses. In addition, physostigmine combats the action of curare on the neuromuscular junction of skeletal muscle. Owing to this action physostigmine was introduced in the treatment of myasthenia gravis. It has been replaced for this purpose by neostigmine.

**Circulatory responses to physostigmine.** In man, physostigmine produces peripheral vasodilatation and a rise in skin temperature. The effect on the pulse rate is not constant, and the data in the literature are not consistent. There appears, however, to be a consensus with regard to large doses. These directly depress the myocardium, and the depressant action is likely independent of the vagus nerve since the action is not blocked by atropine.

**Fate in the body.** Physostigmine is excreted in the urine for the most part. Small amounts appear in the saliva and bile.

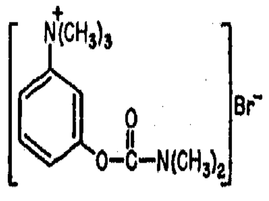
**Toxicology.** Physostigmine in toxic doses produces marked muscular weakness. Consciousness is not lost but often blurred. Nausea, vomiting, and gastrointestinal distress are present. The heart becomes slow in rate, and the blood pressure is lowered. The pupil is markedly constricted. Labored breathing resembling that of asthma may be produced. The drug may also produce convulsions. The cause of death is usually paralysis of the respiratory mechanism.

Atropine is the best physiologic antidote for physostigmine intoxication. Other measures of a supportive nature such as intravenous glucose are indicated.

**The therapeutic uses of physostigmine.** The therapeutic uses of physostigmine are mainly confined to its ocular action. It is used as a myotic in glaucoma and to combat the cycloplegia and mydriasis of atropine when the latter is used for refraction. It is also used alternately with homatropine to prevent the formation of adhesions between the iris and the cornea after certain ocular surgical procedures. For these purposes 0.5 per cent solution of physostigmine salicylate is the solution of choice.

### NEOSTIGMINE (PROSTIGMINE)

**Neostigmine Bromide, U.S.P. (Prostigmine Bromide).** Neostigmine bromide is a synthetic organic compound. It occurs as a white, crystalline powder. It is stable in the air. The compound is soluble in approximately its own weight of water. The structure of neostigmine bromide is shown in the accompanying formula.



Neostigmine Bromide
(Prostigmine bromide)

Neostigmine methylsulfate is also official. The bromide is active upon oral administration; the methylsulfate is administered subcutaneously or intramuscularly.

The chemical formula of neostigmine shows it to be a dimethylaminocarbamic acid ester of oxyphenyltrimethylammonium bromide. By reference to the chemical formula of physostigmine, page 582, it will be observed that this naturally-occurring alkaloid is also a methylaminocarbamic acid ester of oxyphenyl attached to 2 heterocyclic rings. Numerous compounds related to physostigmine were synthesized by Aeschlimann and Reinert (1931). They all contain the carbamic ester group but are devoid of the heterocyclic rings. These substances, of which neostigmine appears to be the most useful, elicit pharmacologically the essential responses of physostigmine. They combine with cholinesterase and serve as cholinergic stimulants. Also they stimulate the contraction of skeletal musculature. Aeschlimann and Stempel (1946) reported their studies on a large number of homologs and analogs of neostigmine. The following findings are of special interest.

1. The replacement of 2 of the methyl groups on the quaternary nitrogen by ethyl groups resulted in a compound highly active on the intestinal musculature but correspondingly more toxic. The efficacy on skeletal muscle was not influenced by the molecular substitution.
2. More toxic neostigmine analogs were prepared by Stevens and Beutel (1941) by increasing the molecular weight by the introduction of alkyl groups into the benzene nucleus. These compounds were active in stimulating paralyzed skeletal muscle but appeared to offer no advantage over neostigmine in their therapeutic index.
3. In general, the compounds of this character which have the highest toxicity evoke the greatest effect on intestinal tone. These also exhibit the highest inhibitory action on cholinesterase. Aeschlimann states, "The correlation is not exact."
4. Moving the position of the carbamic ester to the *ortho* or *para* position on the benzene ring offered no advantage in the activity of the compound.

Randall and Lehman (1950) prepared a series of 20 neostigmine analogs and studied their relative pharmacologic properties. Of this series 3-hydroxyphenyltrimethylammonium bromide (no carbamic acid group) showed strong anticurare action but minimal cholinergic activity. Its toxicity is low. These studies point to the necessity of the carbamic acid group in the neostigmine molecule for cholinergic activity.

The anticurare action of neostigmine appears to be dependent upon the quaternary ammonium group and the carbamate ester. The quaternary nitrogen atom may be a component of a ring structure, as shown in the formula of pyridostigmine, page 589, where it is present in a pyridine nucleus.

**Neostigmine and skeletal muscle.** One of the principal actions of neostigmine is its capacity to stimulate the contraction of skeletal muscle. Upon this action its use in myasthenia gravis depends. Although the stimulating action of neostigmine on the smooth musculature of the intestine is blocked by atropine as was previously stated, page 529, the action of the drug on skeletal muscle is not blocked by atropine. Neostigmine combats the action of curare and certain other skeletal muscle depressants.

Each of the principal actions of neostigmine is mediated mainly through its inactivation of cholinesterase.

**Cholinesterases.** After Loewi and his associates had established that the inhibition of the heart by vagal stimulation was due to the liberation of acetylcholine, they found also an agent in the blood destructive to acetylcholine (Engelhart and Loewi, 1930). This substance was found to be an esterase, quite specific for acetylcholine. For example, the esterase of liver will not hydrolyze acetylcholine. Certain other choline derivatives are hydrolyzed by cholinesterase, but others are refractory to its action.

There are 2 esterases capable of hydrolyzing acetylcholine. One of these is a nonspecific esterase found in various animal tissues such as blood serum, pancreas, and liver. The other is the specific cholinesterase which hydrolyzes only choline esters. This specific or true cholinesterase is found in red blood cells, in the brain, and other nerve tissues. Brain tissues of vertebrates contain only the specific cholinesterase (Mendel and Rudney, 1943).

It has been shown by Koelle and Friedenwald (1949 *et seq.*) that the true and the nonspecific cholinesterases could be readily differentiated in tissues by their relative hydrolytic activities on certain esters under carefully controlled conditions. For example, the nonspecific esterase of cat tissues is almost entirely inhibited by incubation with $10^{-6}$ M di-isopropylfluorophosphate (DFP) at 38°C and pH 6.4 for 30 minutes in the absence of substrate. On the other hand, the specific cholinesterase under the same conditions loses 40 per cent of its original activity. Based upon this and similar findings a histochemical procedure for the localization of the 2 enzymes in the tissues of the cat was developed. With this technic these investigators studied the distribution of the 2 esterases in the tissues of the cat. Regions of the central nervous system examined, skeletal muscle, and smooth muscle were found to contain the true esterase almost exclusively. Sensory ganglia, adrenal pericapsular ganglia, hepatic cells, the carotid body, and other areas of smooth muscle contained mainly the nonspecific cholinesterase. Each type was found in most autonomic ganglia and effector cells. It therefore appears that the nonspecific cholinesterase participates in synaptic transmission similar to that of the true esterase at such sites as autonomic ganglia and effector cells.

Torda (1942) found cholinesterase in tissue without innervation (the human placenta). The cholinesterase in 1 mg. of this tissue is capable of decomposing at 35°C on the average $6 \times 10^3$ $\mu$g. of acetylcholine per second.

Nachmansohn and his associates (1938) have made a study of the distribution of cholinesterase in nerve tissue. They observed that the esterase was found at neuronal surfaces. "The enzyme is highly concentrated in all nerve fibers but the concentration rise at synaptic regions may be referred, partly at least, to the increase in surface at these regions."

There are high concentrations of cholinesterase at motor nerve end plates. The esterase is also present in high concentrations at all ganglionic synapses as well as the synapses of the central nervous system. Thus it is observed, wherever acetylcholine is present to activate nerve tissue to effect transmission of the nerve impulse, cholinesterase is present to deacetylate it and terminate its action. Choline and acetic acid are formed.

This hydrolysis is interesting for at least 3 reasons. First, the deacetylation is irreversible; the free energy decrease is apparently so great that the tissues must use another means of ester resynthesis, namely, *choline acetylase.* Second, the activity drop of acetylcholine to choline is in the order of magnitude of 100,000 to 1. Third, this reaction enables one to measure cholinesterase activity manometrically. The liberated acetic acid is made to react with sodium bicarbonate. Therefore each mole of acetylcholine

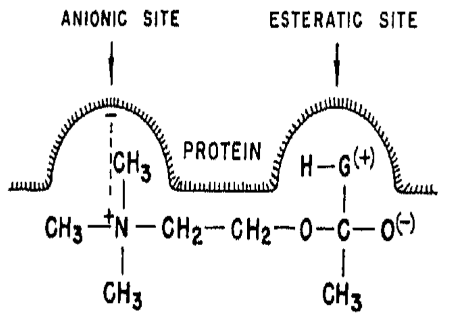


FIG. 36-1. Schematic representation of the principal subsites of acetylcholinesterase. (*Wilson, 1959.*) The incipient hydrogen bond sets off an electronic cycle that results in the splitting off of the alcohol choline and the formation of an acetyl enzyme. The acetyl enzyme reacts with water in a few microseconds to reverse the general process, form the acid, and regenerate the enzyme.

deacetylated will liberate 1 mole of carbon dioxide.

The specific and the nonspecific cholinesterases are inactivated by a large variety of substances. The special interest of the pharmacologist lies in the inhibition produced by physostigmine and its synthetic congeners and di-isopropylfluorophosphate.

Wilson (1959) described the hydrolysis of acetylcholine by cholinesterase schematically as follows. There is an *anionic site* that binds and orients the cationic portion of the substrate. The source of the binding energy is believed to be a net van der Waals' attraction between methyl groups and a hydrocarbon portion of the protein. There is an *esteratic site* $H—G^{(+)}$ containing an essential acidic group represented by a hydrogen atom and a basic group represented by a pair of electrons. Binding here is achieved through a covalent bond between the basic group and the electrophylic carbonyl carbon atom. This arrangement is shown in figure 36-1.

The physostigmine type molecule enters into competitive displacement with acetylcholine for the enzyme surface sites in concentrations as low as $10^{-6}$ M. Straus and Goldstein (1943) showed that 1 molecule of physostigmine and acetylcholine enter into a competitive displacement for the active sites on the surface on the enzyme cholinesterase. Displacement by physostigmine (or neostigmine) nullifies the capacity of the enzyme to hydrolyze acetylcholine.

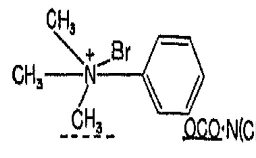
Koelle and Koelle (1959) presented evidence to suggest that the primary role of cholinesterase at autonomic ganglia is the prevention of postsynaptic activation by acetylcholine liberated by the presynaptic fiber during the resting stage. Other functions may include the prevention of accumulation and spread of acetylcholine during the course of repeated presynaptic volleys, and the protection of the presynaptic terminals against the initiation of antidromic firing by acetylcholine. Further evidence was presented by McIsaac *et al.* (1959) to suggest that only external cholinesterase is functionally active in hydrolyzing acetylcholine. The intracellular cholinesterase serves as a reserve source of replacement of the external enzyme.

**The action of neostigmine on skeletal muscle.** The concept of the action of neostigmine in stimulating the contracting of skeletal muscle has been stated. The action was believed to be due to its capacity to inactivate cholinesterase and provide for a more intensified and longer action of acetylcholine. The availability of other agents which specifically inhibit cholinesterase has enabled investigators to put this hypothesis to a rigorous test.

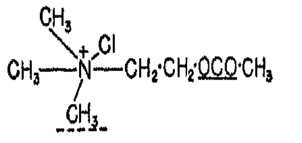
Di-isopropylfluorophosphate (DFP) is a substance which markedly inhibits cholinesterase. Riker and Wescoe (1946) inactivated the cholinesterase in the gastrocnemius-soleus muscles in the cat by intra-arterial injections of DFP into the artery supplying blood to the muscles. The contractile response of the muscles was elicited by acetylcholine in the absence of esterase activity as one would expect. Neostigmine, however, also evokes contraction of the musculature. The response to neostigmine after the inactivation of cholinesterase by DFP was only slightly different from that produced by neostigmine in the normal muscle. These results are illustrated by Riker and Wescoe in figure 36-2.

This work shows that neostigmine mediates its action in at least 2 ways, producing the contraction of skeletal muscle (1) by a direct primary action on skeletal muscle, and (2) by inactivation of cholinesterase. Riker and Wescoe suggest that since the action of neostigmine on skeletal muscle is direct it could properly be classified for pharmacologic purposes with the choline esters. Actually from a chemical standpoint it is a quaternary ammonium compound to which class of substances acetylcholine belongs.

An examination of the 2 following formulas illustrates this spatial similarity in chemical configuration.



Neostigmine Bromide



$$CH_3—\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{\overset{+}{N}}}\!\!{}^{Cl}—CH_2·CH_2·\underline{OCO}·CH_3$$

Acetylcholine Chloride

The *broken lines* show the positive quaternary nitrogen atom and the *solid lines* the ester linkage each common to both molecules.

In addition to the actions of neostigmine on skeletal muscle and inhibiting cholinesterase, Long and Eckstein (1961) showed that the drug was capable of stimulating sympathetic ganglia. Neostigmine evoked a pressor response in dogs following the administration of various competitive ganglionic blocking agents. The pressor response was not elicited by neostigmine following the noncompetitive ganglionic blocking agent tetramethylammonium bromide. The pressor response was antagonized by the adrenergic blocking agents Dibenamine and tolazoline. They further showed that in the presence of

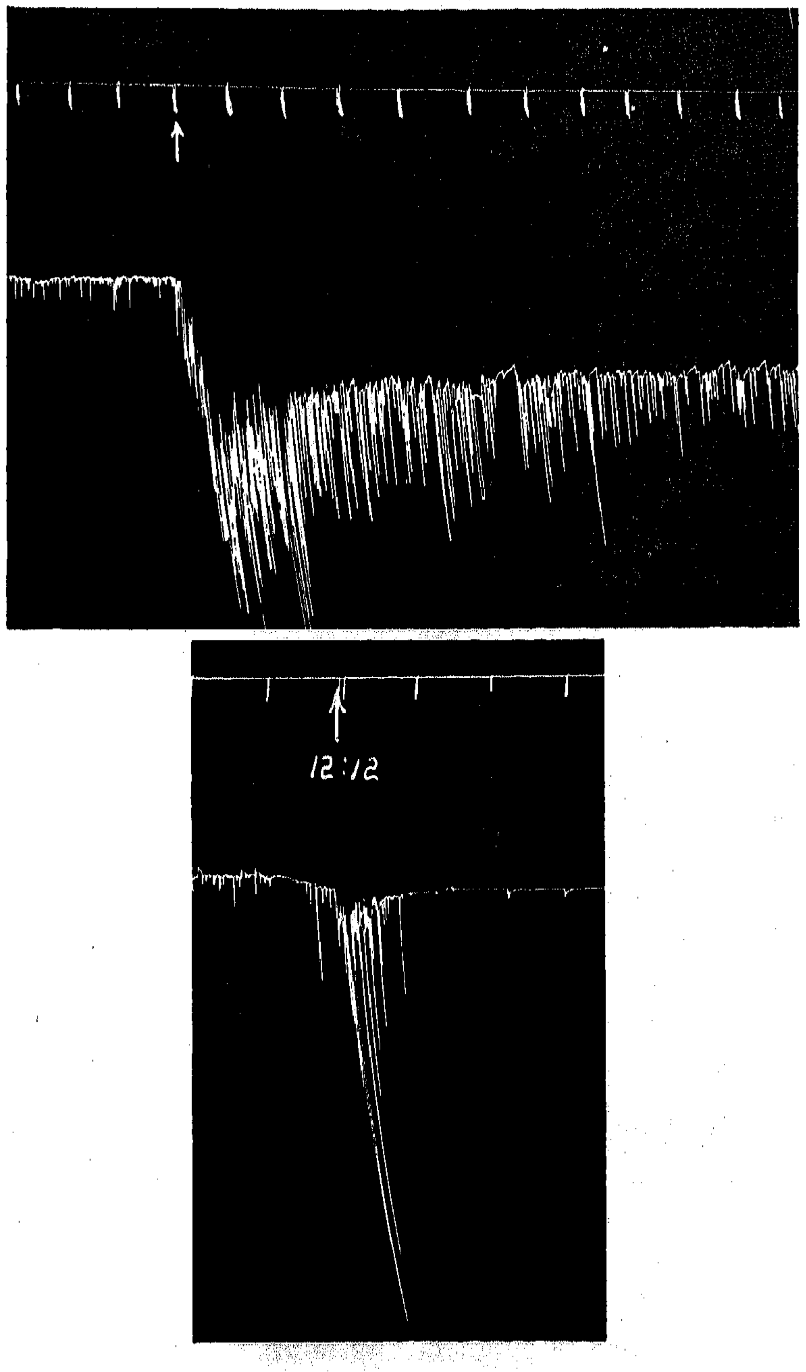


FIG. 36-2. The response of skeletal muscle to neostigmine in the presence and absence of cholinesterase. *Upper tracing:* at *arrow* neostigmine bromide 25 μg./kg. intra-arterially. *Lower tracing:* DFP 1 mg./kg. intra-arterially was given at 12:02. At 12:12 neostigmine bromide 25 μg./kg. intra-arterially. Time intervals: 30 seconds. (*Riker and Wescoe, 1946.*)

ganglionic blockade, neostigmine produced myocardial and peripheral vascular responses similar to those seen with sympathetic nerve stimulation or the administration of catecholamines. Since it is established that epinephrine has a decurarizing action on skeletal muscle, one wonders whether this sympathetic ganglionic stimulant action of neostigmine might not contribute to its beneficial action in myasthenia gravis.

**The therapeutic uses of neostigmine.**

1. Neostigmine is useful in the treatment of myasthenia gravis.
2. Abdominal distension without an obstructive or a perforating element and without peritonitis may be relieved by neostigmine. The parenteral route is preferably 1 ml. of 0.05 per cent solution of the methylsulfate at 2-hour intervals.
3. Neostigmine is valuable in postoperative urinary retention.
4. Neostigmine has been successfully used as a test for pregnancy. If a nonpregnant woman fails to menstruate for psychic or other causes, usually 0.5 to 1 mg. of neostigmine methylsulfate parenterally will induce menstrual flow. It produces hyperemia of the endometrium at the menstrual period.
5. Neostigmine bromide, 7.5 to 15 mg., has been used successfully in antagonizing the constipating action of morphine and codeine. It is claimed to intensity the analgesic action of morphine.
6. In postoperative intestinal atony, neostigmine is the drug of choice. Five-tenths to 1 mg. parenterally is generally used.
7. There are many miscellaneous uses of the drug. In the following conditions it has been used to mitigate symptoms and enjoys a moderate degree of success: (a) Raynaud's disease, (b) rheumatoid arthritis, and (c) anterior poliomyelitis.

### TREATMENT OF MYASTHENIA GRAVIS

**Historical.** Myasthenia gravis is a chronic disease. It is characterized by progressive abnormal fatigability of muscle. The most commonly affected muscles are those of the head and neck. The disease may progress to permanent muscular paralysis. Dysphagia and dysarthria are among the first symptoms. It is estimated that the incidence of myasthenia gravis in the United States (diagnosed and undiagnosed) is approximately 30,000.

In 1930, Harriet Edgeworth, who suffered with myasthenia gravis, published her first paper on the use of ephedrine in the treatment of the disease. She used the drug regularly up to 48 mg. daily and recorded beneficial results. Bülbring and Burn (1938) demonstrated experimentally that the increased tension produced in contractions of the gastrocnemius of the cat, with the nerve stimulated 4 to 6 times per minute, is much greater if ephedrine has been previously injected. Epinephrine apparently produces a decurarizing action against fatigue. This is probably accomplished by decreasing the muscle threshold to acetylcholine. Ephedrine and other sympathomimetic amines impede the destruction of epinephrine and thus synergize its decurarizing action on muscle.

There is a clinical similarity between the loss of skeletal muscle tone in myasthenia gravis and in curare poisoning. This led Mary Walker to conceive the idea that physostigmine, which evoked a decurarizing action, might be useful in the treatment of the disease. In Greenwich in 1934, Walker treated her first patient suffering with myasthenia with physostigmine salicylate. She used 1 mg. subcutaneously. The improvement, which was dramatic, lasted for 2 to 4 hours. This prompted her to continue her studies and the synthetic physostigmine-like compounds were brought to her attention. Walker found neostigmine to be superior to physostigmine.

In 1935, Laurent successfully treated myasthenics with neostigmine. In these patients all other types of therapy appeared to be of little avail. At first the methyl sulfate of neostigmine only was available. It is effective only parenterally. Then the methyl bromide was made available, which is active upon oral administration. Today it is the drug of choice in many cases.

**Etiologic considerations and treatment.** Potassium salts have been suggested in myasthenia based upon the hypothesis that the potassium ion exhibited a "total decurarizing action." The muscle potassium of myasthenics is higher than that of normal individuals (Cumings, 1940). Clinical improvement after neostigmine, according to this investigator, is accompanied by a diminution in muscle potassium and an increase in blood potassium. Later, as the potassium shift returns to high muscle potassium with a corresponding lowering of the blood potassium the symptoms of myasthenia return. Although the use of potassium chloride in myasthenia was considered valuable in former years, the use of this salt even as adjunctive therapy appears to be diminishing.

Attempts to correlate myasthenia with excessive cholinesterase activity and diminished choline acetylase activity of the tissues have been disappointing. Likewise, neither choline nor acetylcholine has been found effective in the treatment of the disease.

Surgical removal of the thymus gland or exposure of the gland to radium emanation has been beneficial in some cases of myasthenia gravis. The procedure was critically reviewed by Eaton and Clagett (1955). From their data the procedure appears to be indicated in younger female patients who do not respond well to drug therapy. In male patients the value of thymectomy has not been demonstrated. Efforts have been made to demonstrate that thymus gland extracts from myasthenic patients have a depressant action upon the contraction of skeletal muscle. The presence of a specific skeletal muscle depressant in the thymus gland of myasthenic patients has not been demonstrated.

The consensus seems to be that myasthenia gravis is a complex disease involving the biochemical reactions of skeletal muscle contraction, manifesting itself as a competitive block at the neuromuscular junction to the depolarizing action of acetylcholine.

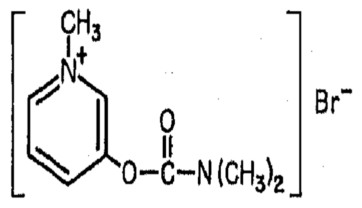
**Neostigmine in myasthenia.** The value of neostigmine in myasthenia gravis is associated with the following actions elicited by the drug:

1. Inactivation of cholinesterase, providing a more intensified and longer action of acetylcholine.
2. Direct stimulating action on skeletal muscle.
3. A shift of muscle potassium to produce a corresponding increase in blood potassium (Cumings, 1940).

Neostigmine methylsulfate when injected subcutaneously or intramuscularly is active when 0.5 mg., 1 ml. of a 0.05 per cent solution is used. Orally, however, 15 mg. of the bromide are required for therapeutic results in myasthenia. The bromide is available in tablets which are administered 3 to 6 times a day. In 85 per cent of the cases the oral administration is effective (Schwab and Chapman, 1947). As tolerance is developed the dose may be increased to 30 mg. 3 to 6 times a day. Goodman (1937) found 30 mg. well tolerated upon repeated dosage; 45 mg., however, caused collapse within 3 hours. The premonitory symptoms were *malaise*, *vertigo*, *salivation*, *tenesmus*, *twitching of skeletal muscles*, and *bradycardia*. Atropine sulfate, 1 mg., caused an amelioration of most of the symptoms. The prolonged use of neostigmine in myasthenia indicates that the drug is not habit-forming since tolerance decreases when patients suffer remission. The drug has a comparatively short period of action and repeated doses are necessary throughout the day. Osserman (1958) has found one-half of a 15-mg. tablet 3 times daily adequate in some cases, whereas as many as 100 tablets a day may be necessary for severe cases. Timespan tablets containing 22.5 and 45 mg. of the drug have offered a partial solution to the problem of frequent medication. The principal disadvantage of neostigmine is that upon prolonged use resistance to its action develops in some patients.

Quinine has a specific harmful effect in myasthenia, and it should be interdicted in individuals suffering with the disease. This alkaloid antagonizes the stimulating effect of acetylcholine in producing the contraction of skeletal muscle. Quinine has been used in the differential diagnosis of myasthenia gravis.

**Pyridostigmine Bromide, U.S.P. (Mestinon Bromide).** Pyridostigmine bromide is an analog of neostigmine, as shown in the formula.



Pyridostigmine Bromide
Mestinon Bromide
(dimethyl carbamic ester of 3-hydroxy-1-methylpyridinium bromide)

Pyridostigmine bromide occurs as a white crystalline powder which is soluble in water and alcohol.

**Pharmacologic action of pyridostigmine bromide.** In a variety of the usual laboratory animals, pyridostigmine was shown to be approximately ⅕ as toxic as neostigmine, and about ¼ to ½ as potent. Thus it appears to have an advantage in showing a higher margin of safety.

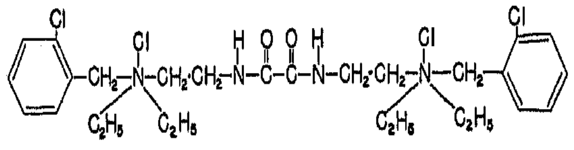
The action of pyridostigmine on the isolated strip of the rabbit's ileum was found to be about ⅛ that of neostigmine, which appears to be a distinct advantage in the diminution of gastrointestinal distress in the therapy of myasthenic patients. The inhibitive activity of pyridostigmine on purified eel cholinesterase preparations was found to be about 1/100 that of neostigmine. The anticurare action of pyridostigmine, as measured on the dog's tibialis anticus, was about ¼ that of neostigmine. The myotic action of neostigmine on the cat's eye, upon instillation into the conjunctival sac, greatly exceeds that of pyridostigmine. In summary, it appears that this analog of neostigmine is a less potent and less toxic agent than neostigmine with a greater therapeutic index.

**Therapeutic use of pyridostigmine.** Pyridostigmine was used in Europe for some time before its introduction into America. Schwab *et al.* (1955) considered the drug less effective than neostigmine in myasthenia gravis. There appears to be a revival of interest in the use of pyridostigmine owing to the fact that the use of this agent in myasthenia permits more intensive therapy, and is less fraught with disconcerting side effects. In addition, the increase in skeletal muscle tone afforded by pyridostigmine is of longer duration than that produced by neostigmine in some patients.

Schwab *et al.* (1957) used pyridostigmine and neostigmine in the treatment of a series of myasthenic patients, using sustained-release tablets. They found this method of medication valuable, and were better able to control the myasthenia during the sleeping hours. They found less gastrointestinal disturbance with pyridostigmine than with neostigmine. In a segment of their patients the longer duration of action of pyridostigmine was confirmed. The usual tablet of pyridostigmine contains 60 mg., and the average daily dose is 10 tablets, although as much as 1.5 gm. of the drug may be necessary daily in severe cases. In the sustained tablet experiments pyridostigmine was made available in tablets of 180 mg. or 3 doses and neostigmine in 45 mg. or 3 doses.

From the clinical data available it is apparent that pyridostigmine has a place in the treatment of myasthenia gravis. The treatment of the disease is highly individualized, and the physician's problem is to select the drug which affords maximal muscle tone with minimal side effects.

**Mytelase Chloride (Ambenonium Chloride).** There have been many attempts to obtain an agent with cholinergic activity similar to neostigmine but with longer activity and minimal gastrointestinal side effects. Mytelase chloride appears useful as a competitor of neostigmine. Mytelase chloride is a complex compound containing 2 quaternary nitrogen atoms as shown in the formula.



Mytelase Chloride

[N,N′-bis (diethylaminoethyl) oxamide-bis-2-chlorobenzyl chloride]

Mytelase chloride is a white crystalline powder which is freely soluble in water.

**Pharmacologic action of Mytelase chloride.** Mytelase chloride is a potent inactivator of cholinesterase. On a weight basis it is 3.2 times more active than neostigmine methylsulfate; on a molar basis the anti-cholinesterase activity is 5.8 times that of neostigmine. Mytelase chloride is more active against the specific cholinesterase than it is against the nonspecific enzyme.

In eliciting the contraction of isolated segments of the rabbit's ileum, Mytelase chloride showed 1/10 the activity of acetylcholine. Mytelase chloride, like neostigmine, potentiates the depressor response to acetylcholine. In these experiments Mytelase chloride appears to be from 50 to 100 times more potent than neostigmine.

Mytelase chloride was shown also to protect mice against the muscle paralysis produced by *d*-tubocurarine. The acute toxicity of Mytelase

chloride in mice was determined to be 5 mg./kg. $LD_{50}$ upon subcutaneous injection compared to 0.53 mg./kg. $LD_{50}$ for neostigmine. Subacute toxicity experiments in rats indicated the availability of Mytelase chloride for clinical trial.

**Therapeutic use of Mytelase chloride.** Schwab *et al.* (1955) used Mytelase chloride in 75 patients with myasthenia gravis. They assert that the anticholinesterase activity is longer than that evoked by neostigmine, and further that treatment is less complicated by annoying side effects. They are of the opinion that the cholinergic activity of Mytelase chloride lasts twice as long as that of neostigmine. Gastric-stimulating responses in their patients were significantly less than with neostigmine. Since gastrointestinal symptoms are a warning to more severe intoxication with cholinergic agents, Mytelase chloride treatment requires supervision in the form of careful dosage control. Of the 75 patients using Mytelase chloride, 59 preferred the drug to neostigmine.

Mytelase chloride is available in 25-mg. tablets. The daily dose in myasthenia varies from 3 to 6 tablets. Schwab found the parenteral dose 1/30 of the oral dose.

Grob (1958) in an extensive literature review of myasthenia gravis and its treatment, compared the effects of neostigmine, pyridostigmine, and Mytelase in over 100 myasthenic patients. The maximal muscle tone afforded after each of these three compounds in optimal doses was approximately the same. The drugs differed mainly in their duration of action and cholinergic side effects. Pyridostigmine and Mytelase were intermediate in their duration of action and danger of overdose. Pyridostigmine appeared to be less likely to produce muscle weakness than Mytelase following over-dosage. Mytelase chloride has apparently warranted a place in the treatment of the myasthenic patient along with neostigmine and its analog, pyridostigmine.

**Cholinergic and myasthenic crises.** The myasthenic patient treated with any of the 3 anticholinesterase drugs must be made aware of the symptoms of over dosage and make contact with the physician should these occur. As has been stated previously, the use of atropine will combat the gastrointestinal symptoms of these cholinergic drugs, but not the skeletal muscle action. In the cholinergic crisis, the same symptoms of marked weakness that prevail in the myasthenic crisis are present. However, in the cholinergic crisis *pallor*, *hypertension*, *bradycardia*, *myosis*, *salivation*, *sweating*, and *muscular fasciculations* are present that do not appear in the myasthenic crisis. Further differentiation may be achieved by the injection intravenously of 1 to 2 mg. of edrophonium (Tensilon). If the patient is improved by the injection the crisis is considered to be myasthenic. Any other response such as exacerbation symptoms indicates a cholinergic crisis (Osserman, 1958).

In the cholinergic crisis the multifaceted pharmacologic response to acetylcholine becomes manifest in the symptoms. The muscarinic action of acetylcholine is evinced by the *gastrointestinal symptoms*, *nausea*, *vomiting* and *tenesmus. Dyspnea*, *bradycardia*, *sweating*, and *myosis* are also classical signs. These are combated by the use of atropine. The nicotinic action of acetylcholine is manifested by muscular fasciculations, twitchings, and generalized fatiguability. When the anticholinesterase drugs are given in excess, a plethora of acetylcholine, present at the neuromuscular junction, provokes a depolarizing block of skeletal muscle. This gives rise to the extreme weakness, and this in turn, resembles the weakness of myasthenia.

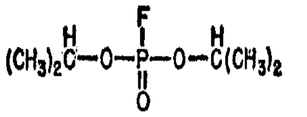
**Treatment of anticholinesterase intoxication.** It has been mentioned that any of the anticholinesterase drugs, such as neostigmine, may produce intoxication by the production of the so-called *cholinergic crisis*. The syndrome is marked by *increased activity of smooth muscle and secretory glands* (*nausea*, *vomiting*, *diarrhea*, *sweating*, and *increased salivary and bronchial secretion*), *bradycardia*, *central nervous system symptoms*, *muscular weakness*, and *fasciculations*. The administration of large doses of atropine will combat the toxic effects of cholinergic agents which are attributable to excess parasympathetic activity, but it has no influence on the muscular weakness which may result in respiratory arrest owing to the failure of the muscles of respiration. Wilson and Ginsburg (1955) showed that the neuromuscular block produced by anticholinesterase compounds in laboratory animals could be reversed by certain oximes. Two of these agents have been used clinically to reverse cholinesterase inhibition and the concomitant neuromuscular blockade caused by organophosphorus or quaternary ammonium anticholinesterase compounds. These oximes are pyridine-2-aldoxime (2-PAM) and diacetyl monoxime (DAM).

Grob (1958) observed that the intravenous administration of 1000 to 2000 mg. of either 2-PAM or DAM caused a rapid amelioration of the generalized weakness elicited by over dosage of organophosphorus or quaternary ammonium anticholinesterase drugs in normal persons and myasthenic patients. They have served as a valuable adjunct to atropine therapy in some cases which, as stated previously, does not combat the muscular weakness of the cholinergic crisis. In the myasthenic patient, caution must be enjoined in the use of the oximes, as overdosage of the oxime returns the muscle strength to the basal level present before the administration of the anticholinesterase drug. The use of the oximes is valuable in reducing the time necessary to administer artificial respiration and to continue endotracheal intubation in the cholinergic crisis.

Osserman and Genkins (1963) evaluated the use of these anticholinesterase drugs and other measures in their series of myasthenic or cholinergic crises since 1958. They have observed 47 crises in 35 patients in this period. Their emphasis has changed from the use of more and more anticholinesterase in the treatment of crisis to less and less drugs. The early performance of tracheotomy with mechanically assisted respiration and with the withdrawal of all drugs for about 72 hours has been beneficial. The mortality in crisis was reduced from 29 in 67 cases, to 8 deaths in 47 crises over the past 4 years. They state that their experience with PAM has been relatively disappointing. They found only partial reversal of respiratory arrest achieved by the drug in the patient with a cholinergic crisis. Besides, the effects appear too evanescent, lasting 3 to 4 hours, whereas the toxic respiratory effects in the cholinergic crisis last about 72 hours. It is clear that if drug therapy is to play an important role in the cholinergic crisis, a more effective drug is required.

## Miscellaneous Parasympathomimetic Drugs

**Isofluorophate, U.S.P. Di-isopropylfluorophosphate (DFP).** DFP has been mentioned previously as a specific inhibitor of cholinesterase. Hence it is capable of producing stimulation of cholinergic fibers by allowing a more intensified and longer action of acetylcholine. The structure of DFP is shown in the accompanying formula.



$$(CH_3)_2\overset{H}{C}{-}O{-}\overset{F}{\underset{O}{\overset{|}{\underset{\|}{P}}}}{-}O{-}\overset{H}{C}(CH_3)_2$$

Di-isopropylfluorophosphate (DFP)

DFP is a clear, colorless or faintly yellow liquid. It is only sparingly soluble in water, but readily soluble in vegetable oils. The vapors of DFP are very irritating to the eyes and mucous membranes.

Lange and von Kreuger (1932) discovered that the alkyl esters of fluorophosphoric acid were irritating to the membranes of the throat and eye in low concentrations. McCombie and Saunders (1946) synthesized many homologs of these esters. DFP appeared to be one of the most promising as a lethal agent in chemical warfare. Mackworth and Webb (1948) made the observation that DFP inhibited cholinesterase. The toxicologic actions of DFP were studied in over 200 cats by Modell *et al.* (1946). In summary these investigators state:

> "The inactivation of cholinesterase is the major action of DFP, but there are other actions which may or may not be secondary to this, which play a part in its toxic effects. While death from moderate doses seems to be related to the 'muscarine-like' actions since it is prevented by atropine, the fatal outcome after massive doses in 'protected' animals seems to involve a combination of central and peripheral paralysis of a nature similar to that of nicotine."

DFP inactivates cholinesterase irreversibly. The inhibition of the esterase by neostigmine is reversible. One would expect therefore that DFP would provide a longer acetylcholine action. This is apparently true and has therefore prompted the use of DFP in therapeutics.

**The therapeutic uses of DFP.**

1. Leopold and Comroe (1946) observed that a solution of DFP 0.1 per cent in oil combated the mydriasis and cycloplegia of a 4 per cent solution of homotropine hydrobromide when instilled into the conjunctival sac. As a myotic DFP appears to be more potent than physostigmine or pilocarpine. Its use in glaucoma was suggested.

   Comroe found that 0.05 to 0.1 per cent of DFP in oil when instilled into the conjunctival sac reduced intraocular tension and produced a well-constricted pupil. Its action is prolonged. Seldom is it necessary to use the drug more than twice daily. In certain cases the myosis was detectable after 27 days. The ocular use of DFP is not without its hazards. Abraham (1953) observed local iris cysts and generalized toxicity consisting of nausea, staggering gait, and enuresis in 2 children after the use of the oil solution. The solution employed was 0.005 to 0.02 per cent.

   This drug appears to be the most powerful myotic available in therapeutics. Its use is accompanied by some temporary blurring of vision and ocular pain. Usually 1 to 3 drops of the oil solution of DFP 0.01 to 0.1 per cent is instilled into the eye every 8 to 72 hours. It is most conveniently administered just prior to retiring. It is unfortunate that DFP is so irritating to membranes and systemically toxic.
2. The use of DFP in myasthenia gravis has been disappointing. It has been given intramuscularly, 2 mg., and orally, 8 mg. Its use is not devoid of such toxic manifestations as nausea, emesis, and diarrhea. Besides, its effects are not so dependable as those of neostigmine.

**Demecarium Bromide, Humorsol.** Humorsol is an 0.25 per cent solution of demecarium bromide used in the treatment of glaucoma and accomodative convergent strabismus (accomodative esotropia). Chemically the agent is N,N′-bis[3-trimethylammoniumphenoxycarbonyl]-N, N′-dimethyldecamethylenediamine dibromide. The compound is a powerful inactivator of cholinesterase. It is more potent and more sustained in its action than neostigmine, physostigmine or DFP. Humorsol is relatively nonirritating, with a pH of 5.5 to 7.0, and is isotonic with conjunctival fluids.

The solution is instilled into the conjunctival sac in dosage ranges from 1 to 2 drops twice a week to twice a day. Humorsol is effective within a few hours. It is particularly recommended in cases of glaucoma that do not respond to the other myotics.

Humorsol may produce local side effects that are very annoying. These include marked myosis, spasm of accommodation with the attendant symptoms of browache, headache, photophobia, myopia and blurred vision, twitching of the eyelids, dilatation of the conjunctival and intraocular vessels, iridocyclitis, pigment cysts of the iris, and, rarely, retinal detachment. Systemic effects of cholinergic symptoms may be evident through absorption owing to prolonged contact with mucous membranes and skin. If these symptoms occur they may be effectively treated with atropine.

The use of Humorsol requires constant vigilance on the part of the oculist for possible development of cysts of the iris and the occurrence of systemic toxicity. The drug is not recommended in glaucoma unless less toxic drugs such as pilocarpine have failed to provide adequate relief.

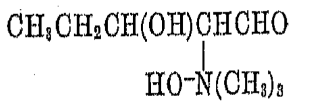
**Echothiaphate Iodide, Phospholine Iodide.** This compound is another long-acting cholinesterase inhibitor similar to isofluorophate, used to reduce intraocular tension in glaucoma.

Chemically, the compound is O, O-diethyl-S-(2-dimethylaminoethyl) phosphorathiolate methyl iodide. It is provided in powder form for solution 0.06 to 0.25 per cent in an aqueous solvent provided by the manufacturer for instillation into the conjunctival sac. Aqueous solutions are relatively stable if refrigerated, but deteriorate at a rate of about 10 per cent a month at room temperature.

A single drop of a 0.06 to 0.125 per cent solution is instilled into the eye daily or on alternate days, usually at bedtime.

Ciliary spasm is the most common side effect encountered with Phospholine iodide solution. Iris cysts and fibrinous iritis may also occur. The drug should be used with the greatest of care in cases with a history of retinal detachment. The use of Phospholine is reserved for cases of glaucoma that do not respond to treatment with pilocarpine.

**Muscarine.** Muscarine is an alkaloid found in the poisonous mushroom *Amanita muscaria.* It is a choline derivative, as shown by the accompanying formula.



$$CH_3CH_2CH(OH)\underset{HO{-}N(CH_3)_3}{\underset{|}{C}}HCHO$$

Muscarine

Muscarine has no therapeutic application. Like acetylcholine it stimulates the activity of the effector cells in organs innervated by cholinergic nerves. Unlike acetylcholine it does not stimulate the contraction of skeletal muscle nor does it act upon the autonomic ganglia.

The toxic action in this type of mushroom poisoning is due to the cholinergic action of muscarine. It is effectively blocked by atropine.

**Arecoline.** Arecoline is one of the alkaloids obtained from the betel nut (*Areca catechu*). Its action resembles that of pilocarpine. It is more powerful and exerts a stronger action on the central nervous system. The alkaloid has not been used in human medicine. The areca nut and the alkaloid, however, are used as laxatives and vermifuges in veterinary medicine.

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# 37

# *Parasympathetic Division of the Autonomic Nervous System (Cholinergic Blocking Agents)*

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### INTRODUCTION

The preceding chapter was concerned with cholinergic agents, *i.e.*, those compounds that mimic the action of acetylcholine on the autonomic nervous system. This chapter discusses those agents that block the action of acetylcholine on the autonomic nervous system. The blockade can occur in the autonomic ganglia, thus blocking the "nicotinic" action of acetylcholine. It can take place at the neuromuscular junction of the cholinergic fibers and the effector sites in smooth muscle, thus blocking the "muscarinic" action of acetylcholine. Of the two sites of blockade, the latter is the more effective and generally the one that predominates with cholinergic blocking agents.

**The nature of cholinergic blockade.** One of the most effective cholinergic blocking agents at the neuromuscular junction is the alkaloid atropine. The mechanism of cholinergic blockade by atropine and its congeners is not clearly understood. There are, however, several interesting facts which have been established by various investigators which indicate that the blockade is achieved by *competitive inhibition* between atropine and acetylcholine for the receptor sites in the effector cells. First, it has been shown that atropine does not inhibit the synthesis of acetylcholine by *choline acetylase*. Second, it has been demonstrated that its action is not mediated by enhancing the action of *cholinesterase* in hydrolyzing acetylcholine. Third, the action of atropine is not on the cholinergic nerve endings, as was formerly supposed. This has been demonstrated by establishing the fact that atropine produces its blockade of acetylcholine in denervated cholinergic organs after the complete degeneration of the postganglionic cholinergic fibers.

In the preceding chapters it was pointed out that the molecule of acetylcholine was characterized by a quaternary nitrogen atom and an ester linkage which are separated at an optimal distance in the molecule. Through these two prosthetic groups it is believed that acetylcholine achieved its attachment to the receptor sites. Atropine contains the ester linkage and a nitrogen atom with approximately the same optimal space between them in the molecule. It is true that the nitrogen atom in atropine is tertiary and that in acetylcholine is quaternary. However, when the nitrogen atom of atropine is quaternized, as in *Eumydrin* (atropine methyl iodide), its potency as a cholinergic blocking agent is enhanced (Ing *et al.*, 1945). This fact lends support to the competitive inhibition hypothesis of the atropine cholinergic blockade. Kunkel *et al.* (1957) studied the pharmacologic response to a quaternary atropine, namely N-benzyl atropinium chloride. Of special interest was their observation that this compound blocked the stimulation of skeletal muscle induced by acetylcholine. It also blocked the transmission of excitation to the nictitating membrane from the preto the postganglionic fibers of the superior cervical ganglion. This agent evokes the antinicotinic properties which are not exhibited by the administration of atropine.

Pfeiffer (1948) suggested that the atropine molecule presents its prosthetic groups in a "center ridge of a large umbrella-like molecule." Thus blockade of the receptor sites to acetylcholine is effected. In addition, the molecule degradates slowly, prolonging the blockade.

### THE BELLADONNA FAMILY

Plants in the potato or *Solanaceae* family contain alkaloids of similar chemical constitution which dilate the pupil. They are therefore commonly referred to as the *mydriatic alkaloids*. The three plants of this group which have medicinal value are *Atropa belladonna* (deadly night-shade), *Hyoscyamus niger* (henbane), and *Datura stramonium* (jimson weed). Belladonna and hyoscyamus grow in England and Central Europe. Stramonium grows abundantly in the eastern section of the United States.

Stramonium leaves and extractive preparations made therefrom are no longer widely used in medicine. Hyoscyamus in the form of its extract and tincture is still prescribed. The leaves contain 0.04 per cent of the alkaloids of hyoscyamus, which are mainly hyoscyamine and hyoscine. On the other hand, belladonna leaves contain 0.35 per cent of alkaloids. There appears to be no therapeutic aim that is accomplished by hyoscyamus which cannot be more effectively achieved by the administration of belladonna. We therefore hold the view that hyoscyamus serves only as a belladonna substitute, and because of the small alkaloidal content of the former, belladonna and its preparations should be given preference.

## Belladonna Leaves, U.S.P.

Belladonna leaves are obtained from the *Atropa belladonna* plant. It was named *bella donna*, beautiful woman, because the drug was used by the female to produce mydriasis for cosmetic purposes. Owing to its poisonous nature Linneaus called it *Atropa* after Atropos, the eldest of the Three Fates, the one responsible for the cutting of the "thread of life." The local action of the drug in the eye, producing mydriasis, was discovered accidentally in 1776 by Daries, a drug clerk of Hamburg, who inadvertently rubbed some of the extract into his eye.

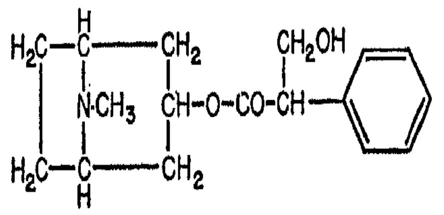
The plant is a bushy perennial which grows to a height of 1 to 1.5 meters. The alkaloids are present in the root as well as the leaves. Formerly the root was also extensively used to make extractive preparations. The principal alkaloids of belladonna are atropine, hyoscyamine, scopolamine (hyoscine), and others of minor importance.

The most important alkaloid of belladonna is atropine. It probably does not pre-exist in the plant but is formed from its isomer hyoscyamine in the extraction process. Atropine is now prepared synthetically also.

Hyoscyamine is the levo-isomer of which atropine is the *dl*-compound. Hyoscyamine is more potent than atropine. The former very readily racemizes to form atropine. A segment of the gastroenterologists prefers the combined alkaloids of belladonna to atropine. Many such preparations are available and are used extensively, and although crucial evidence of superiority of the combined alkaloids does not appear, there is certainly the possibility that the combination of alkaloids may provide more adequate relief in a segment of patients than is provided by atropine alone.

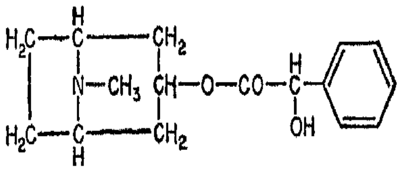
### Chemical constitution and action of the belladonna alkaloids.

*Atropine* is a derivative of *tropane*, a nucleus found in many alkaloids. When tropanol (hydroxytropane) is esterified with tropic acid atropine is formed. Its structure is shown in the accompanying formula.



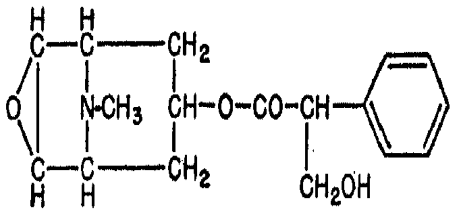
Tropanol Tropic Acid Radical
Atropine
(Tropanyl Tropate)

It will be observed that tropic acid is $\alpha$-phenyl-$\beta$-hydroxypropionic acid; furthermore the alpha carbon atom of this acid is asymmetric. The most useful derivatives of tropanol result from the esterification of this base with an acid which contains an asymmetric carbon atom. The most important of these is homatropine, which contains the tropanol molecule esterified with phenylglycolic acid (mandelic acid) of the constitution shown in the formula below:



Tropanol Mandelic Acid Radical
Homatropine

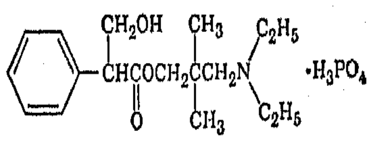
*Scopolamine* (*hyoscine*) is found in belladonna and also in *Datura metel*. It is closely related to atropine chemically. In it the tropanol nucleus contains an ether linkage, as shown in the formula below:



Oscine Tropic Acid Radical
Scopolamine (Hyoscine)

The molecular changes confer interesting pharmacologic properties on the atropine molecule. Homatropine resembles atropine in most of its pharmacologic actions. In the eye the mydriasis and cycloplegia produced by homatropine are less marked and of shorter duration. It is therefore very valuable for refraction. Scopolamine mimics the peripheral action of atropine, but centrally its action is antagonistic to atropine. Large doses of atropine stimulate the cerebrum. Scopolamine produces depression, blurred consciousness, amnesia, and general sedation.

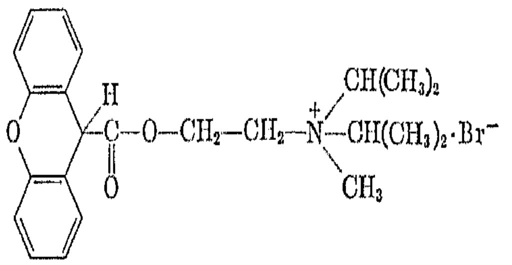
Many more simple derivatives of atropine have been prepared. Some of these are valuable for special clinical purposes. This is illustrated in the molecule of *Syntropan* studied by Fromherz (1937).



Syntropan
(3-diethylamino-2,2-dimethylpropyl
tropate phosphate)

This substance exhibits a strong atropine action on the gut but is only $1/1000$ to $1/100$ as active as atropine on the cardiac vagus or on the pupil and ciliary muscle.

The congeners of atropine may be readily divided into two classes. The first class is represented by the molecule of Syntropan, in which the nitrogen atom is tertiary. This activity is atropine-like in character and confined to muscarinic blockade. The second class contains a quaternized nitrogen atom and evokes muscarinic blockade at the neuromuscular junction and nicotinic blockade at the autonomic ganglia. A prototype of this series is propantheline bromide, as shown in the formula:



Propantheline Bromide
Pro-Banthine

Although theoretically it would appear that the double blockade of the parasympathetic fiber would be advantageous, practically this has not been established. It appears that many times the tolerated therapeutic dose is required to achieve the ganglionic blockade in addition to the neuromuscular blockade. It must be recognized, however, that the agents of this class are often more powerful cholinergic blocking agents of the muscarinic type than those containing tertiary nitrogen atoms. Thus in some cases in which the atropine-like tertiary nitrogen atom compound has failed, they achieve relief used as antispasmodics.

### Atropine.

**Atropine Sulfate, U.S.P.,** is the sulfate of the principal alkaloid of belladonna. It is also prepared synthetically. Atropine sulfate occurs as colorless crystals or as a white, crystalline powder. One gm. of the salt is soluble in 0.5 ml. of water and in 5 ml. of alcohol. Aqueous solutions of atropine sulfate are slightly acid, pH 5.4. They are stable for long periods of time.

**Response of the central nervous system to atropine.** In the usual therapeutic doses, 0.5 to 1 mg., atropine produces no demonstrable effects upon the central nervous system when this system has not been previously depressed. In larger doses, 2 to 4 mg., atropine stimulates the cells of the cerebral cortex. The effect resembles that of caffeine or the release from inhibitions produced by alcohol. The cerebral toxic syndrome of atropine is similar to alcoholic inebriety. The individual becomes loquacious, restive, disoriented, and may experience hallucinations. Maniacal behavior may follow large doses of the drug.

Mental alacrity is not usually increased, as is the case with caffeine. The motor as well as the sensory areas of the brain are stimulated, and uncontrollable motor activity may result. Koppanyi (1939) observed that small doses of atropine synergized the action of the aliphatic narcotics on the motor areas of the brain. Larger doses, however, were capable of reversing this activity, as demonstrated by the synergizing of the action of the spinal convulsants.

The stimulation of the cerebral cortex continues until the individual is exhausted from the repetitious stimuli reaching the higher centers. This is followed by depression, stupor, and coma.

Marrazzi *et al.* (1951) demonstrated that atropine was capable of blocking the transmission of the nerve impulse at a synapse in the brain just as it functions to block the transmission of the nerve impulse at autonomic ganglia. They exposed the preganglionic fibers of the optic nerve of the cat to submaximal electrical stimuli. They recorded the stimuli by the electrical effects which they established in the visual cortex. Acetylcholine injections into the circulation produced similar results. The effects produced were blocked by the injection of atropine. This demonstrated the capacity of atropine to block the cerebral synapse which, like the autonomic synapse, depends upon acetylcholine for transmission.

The respiratory mechanism is stimulated by small doses of atropine. This is particularly manifest if the respiration has been previously depressed by a narcotic drug. The preliminary respiratory stimulation from small doses of atropine is followed by marked depression if the drug is given repeatedly. This is notably true in morphine poisoning (see page 358). Doses of atropine up to 1 mg. antagonize the depressant action of morphine on the centers of respiration; larger and repeated doses of the drug actually synergize the depression of morphine. When atropine kills, the cause of death is the depression and ultimate paralysis of the centers of respiration. Miyazawa (1956) observed that in mice *atropanal* evoked severe convulsions and persistent respiratory activity, which were suppressed by small doses of atropine. Large doses of atropine elicited a central nervous system syndrome similar to that produced by atropanal. He suggests, as indicated by his experiments, that the central stimulating action of atropine, but not its peripheral effects, may be attributed to its partial conversion to atropanal.

The spinal cord is not demonstrably affected by therapeutic doses of atropine. Large doses produce stimulation which results in muscular twitchings.

The use of atropine in parkinsonism has been discussed on page 431. Atropine has been used to induce periods of excitation in schizophrenic patients. Massive doses are required (Forrer, 1951).

**Action on the circulation.** It has been stated previously (see page 531), that atropine blocks the vagal stimulating action of acetylcholine and other choline esters. Furthermore, it obliterates the peripheral vasodilating action of acetylcholine. The precipitous fall in blood pressure produced by an intravenous injection of acetylcholine in a laboratory animal is completely nullified by the previous injection of atropine. The injection of atropine alone is far less dramatic in its action on the circulation than one would anticipate from its capacity to antagonize the powerful depressor action of acetylcholine.

Marrazzi (1939) has demonstrated not only that atropine blocks the action of acetylcholine at the effector cells innervated by cholinergic fibers, but also that in larger doses the blocking occurs at all autonomic ganglia. It will be recalled that at the autonomic ganglia, acetylcholine is the substance responsible for the transmission of the nerve impulse from the pre- to the postganglionic fibers.

On the circulation, as on the respiration, the effect of atropine is a function of dose. Small doses of atropine, 0.5 to 0.6 mg., stimulate the vagus centrally, and the pulse is generally slowed slightly by this action. This is the common effect experienced with the usual clinical doses of atropine. Larger doses of the drug, 1 to 2 mg., depress the vagus peripherally, and the central slowing action is masked by a partial escape of the heart from vagal inhibition. The effect of atropine on the cardiac vagus is sufficient to prevent vagal inhibition of the heart even by strong electrical stimulation of the vagus. Thus one finds that atropine abolishes the cardiac slowing produced by:

1. Ammonia (reflex stimulation of vagal center)
2. Picrotoxin (direct stimulation of vagal center)
3. Nicotine (stimulation of the vagal ganglion)
4. Neostigmine (inhibition of cholinesterase in cardiac effector cells)
5. Acetylcholine (direct stimulation of vagal cardiac effector cells)

The effect of atropine upon the pulse rate is dependent upon vagal tone. In infancy and old age, when vagal tone is less, atropine produced less effect upon the pulse rate. He found the slowing effect of atropine on the pulse less marked in the Negro than in the white race.

It has been shown that the atrial fibrillation which is induced by the local application of acetylcholine to the right atrium of the dog's heart is abolished by the local application of atropine, with the subsequent restoration of normal cardiac rhythm (Botti and Visioli, 1958).

Therapeutic doses of atropine produce no significant changes in blood pressure. Larger doses of the drug elicit a rise in blood pressure. The pressure rises as a result of the central stimulation of the vasoconstrictor center and the increase in pulse rate, owing to vagal inhibition. The cardiac output per beat is unaltered, but the minute output is increased.

Constriction of the blood vessels occurs only in the splanchnic area. The cutaneous vessels are dilated by large doses of atropine. This is especially noticeable in the blush area. Repeated dosage may cause desquamation of the epidermis, and the syndrome resembles *scarlatina*. The dilatation of the cutaneous vessels in the face appears to be central in origin also, since it is obliterated by the severance of the sympathetic nerves in the neck.

Atropine is used in 2-mg. doses intramuscularly to antidote poisoning with anticholinesterase compounds. Kalser *et al.* (1954) observed that this dose of atropine produces postural hypotension caused by peripheral vascular pooling. The simultaneous compression of both legs and abdomen was found to be effective in preventing postural hypotension. They suggest that the hypotension is the result of partial vagal block, partial ganglionic block, and central excitation.

Very large or repeated small doses of atropine ultimately cause a fall in blood pressure after the preliminary rise. This also resembles the action of atropine on the respiratory centers, where small doses stimulate and large doses depress. The larger doses of the drug depress the vasoconstrictor center, giving rise to peripheral vasodilatation.

**Effect on the bronchi.** The cholinergic nerves are motor and secretory to the bronchi. Therefore a drug like atropine, which blocks cholinergic activity, serves to dilate the bronchioles and to diminish the secretion of mucus. For many years the drugs of the belladonna family were the principal agents used in the treatment of asthma. Belladonna, stramonium, lobelia, hyoscyamus, and other drugs were mixed. To these was added potassium nitrate to effect combustion. The mixtures were designated as "asthma powders." They may be rolled into cigarettes and the smoke inhaled in the usual manner. When it was ignited and the smoke was inhaled, the asthma powder or cigarette brought the alkaloids or their products of partial combustion in direct contact with the bronchioles of the asthmatic patient. Often relief was acquired by such medication. However, today these asthmatic powders have been replaced largely by drugs which are more rapid and dependable in their action, such as epinephrine.

In asthma there occurs a spontaneous contraction of the bronchioles. The lumen is narrowed further by catarrhal swelling of the mucosa. This narrowing of the air passages is especially marked upon expiration and is aggravated by the rise in intrathoracic pressure. The lungs are distended, and the blocked passage of the air gives rise to emphysema.

Atropine is useful; 1 mg. subcutaneously often gives prompt relief. However, epinephrine, which stimulates adrenergic activity and dilates the bronchioles, is more prompt in relieving the asthmatic spasm. Since the cholinergic fibers to the bronchi are both motor and secretory, atropine blocks not only bronchiolar constriction but also mucus secretion. The latter action renders the expulsion of mucus more difficult and may give rise to mucus plugs and bronchiolar obstruction. Now that epinephrine throat sprays and corticosteroids are in use, atropine, asthmatic powders, and asthma cigarettes have largely been replaced by these more dependable medicinal agents.

**Effect on the gastrointestinal tract.** The cholinergic nerves are motor and secretory to the stomach and motor to the intestines. We have seen how neostigmine and physostigmine enhance gastrointestinal activity. Atropine is capable of blocking the action of cholinergic drugs on the gastrointestinal tract. It will lessen the motor activity and tranquilize the hypermotility of an excessively active gastrointestinal tract. This is one of the most important and clinically useful actions of atropine. Like the response of other systems to the action of atropine, the effect on the gastrointestinal tract is a function of dose. Kay and Smith (1956) found that the injection of 0.1 mg. of atropine stimulated gastric motility, whereas 0.65 mg. of the drug inhibited the gastric movements. The simultaneous administration of hexamethonium chloride (autonomic ganglionic blockade) blocked the stimulating action of small doses of atropine. The effect of atropine upon the isolated strip of a rat's small intestine is shown in figure 37-1.

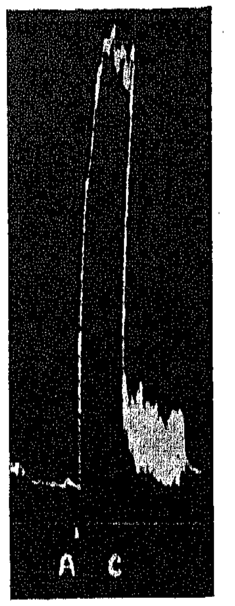


FIG. 37-1. The effect of atropine on the isolated strip of rat's intestine. *A*, barium chloride; *C*, atropine. (From J. C. Krantz, Jr., J. W. Forrest, and C. K. Heisse, Proc. Soc. Exper. Biol. & Med., **86:** 511, 1954.)

Small doses of atropine are useful in diminishing gastric secretion in peptic ulcer. Sanotzky (1892) was likely the first to show that atropine inhibited not only gastric motility but also the secretion of gastric juice which results from the introduction of food into a dog's stomach. Vagal inhibition affects the phases of gastric secretion in varying degrees. It follows, therefore, that since atropine functions through this mechanism its action would follow the same course. Thus the cephalic or nervous phase of gastric secretion, which appears to be entirely under vagal control, is markedly depressed by atropine. The volume is diminished more than the acidity. The second phase of gastric secretion, which is hormonal in character and initiated by the release of gastrin from the *pyloric* antrum, is not so effectively in-

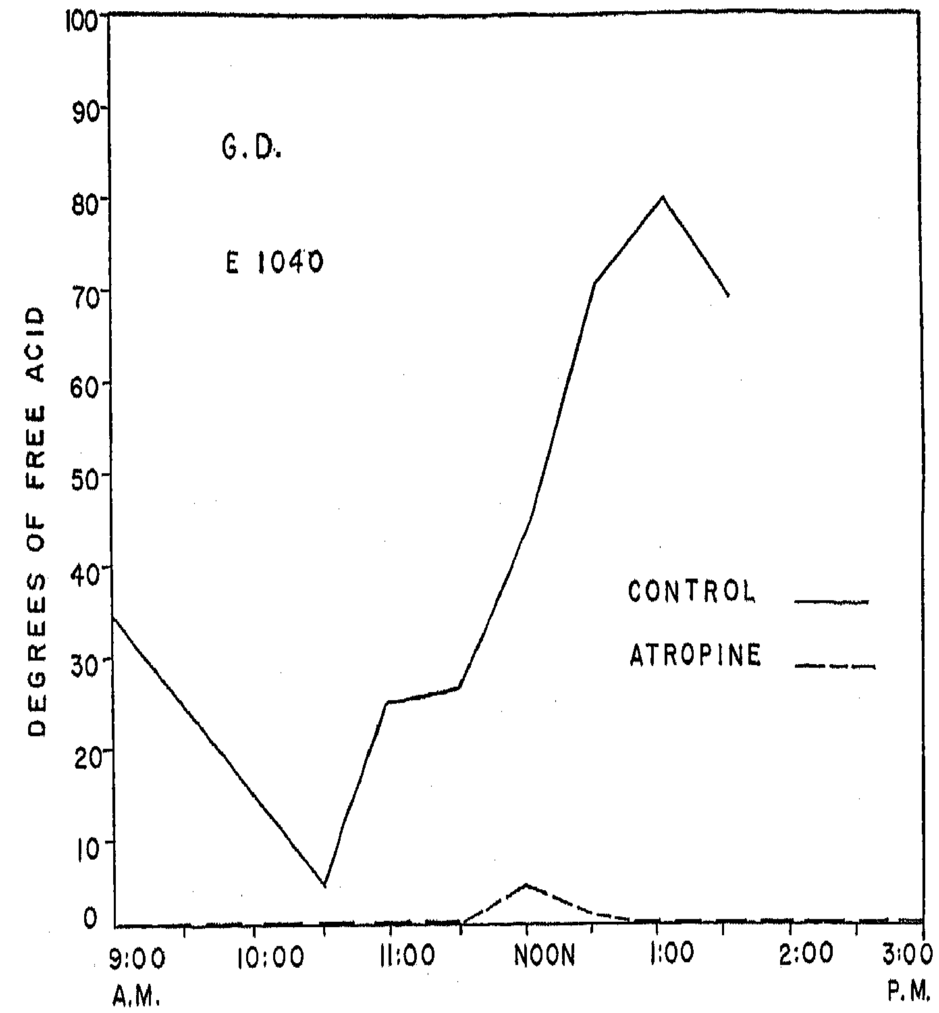


FIG. 37-2. The effect of giving atropine intravenously on gastric secretion. Motor meal of 100 ml. of 7 per cent alcohol was followed by a steady increase of free HCl, which reached a maximum of 80° in 4 hours. Two days later 1.3 mg. of atropine sulfate was injected intravenously at the time that the motor meal was given by stomach tube. Achlorhydria resulted and persisted for 5 hours, or until the stomach was empty. (From W. D. Paul and C. Rhomberg, J. Iowa M. Soc., May, 1945.)

hibited by atropine as the secretion under vagal control.

Wolf and Wolff (1943) found that doses of atropine from 0.6 to 2.4 mg. inhibited gastric contractions, parietal cell secretion, and also the secretion of mucus. Paul and Rhomberg (1945) administered a test meal to an individual and measured the secreted gastric acidity. Subsequently the same procedure was repeated, and atropine sulfate was administered intravenously at the time the meal was given. The results are shown in figure 37-2.

The results obtained by repeated administration of atropine, along with a plain diet, in uncomplicated cases of peptic ulcer are shown by the data of Paul and Rhomberg (1945) (fig. 37-3).

Notwithstanding the numerous atropine-like, synthetic antispasmodics used on the gastrointestinal tract, atropine still appears to be the drug of choice. The principal action of atropine on the gastrointestinal tract is on the small intestine and the stomach. Muscular tonus and peristalsis are decreased by the administration of atropine. Its effect is less marked upon the motility of the colon. Ulcer patients may take the drug daily for years in very small doses with excellent results. Tolerance does not usually develop, and untoward effects such as xerostomia are minor in character. Gray and Seevers (1955) observed that frequently repeated administrations of atropine in dogs produced rapidly diminishing activity on intestinal motility. Of special interest was the fact that cholinergic blockade in the intestine was found to persist for a considerable period after tolerance to the action had been established. Only those intestinal spasmolytics which mediate their action through cholinergic blockade exhibited tachyphylaxis in the intestine.

It is indeed surprising how oral doses of atropine as small as 0.25 to 0.5 mg. give very satisfactory results in tranquilizing hypermotility of the gastrointestinal tract. Atropine is particularly useful in peptic ulcer when pylorospasm is present. Atropine promptly diminishes the spasticity and mitigates the concomitant referred pain.

Chapman *et al.* (1950) studied the effect of various antispasmodics upon the motility of the upper portion of the small intestine in man. They made their recordings by means of a multiple balloon water manometer system. The drugs were administered in the usual therapeutic doses. Atropine, 0.45 to 0.6 mg., or 20 drops of belladonna tincture produced a decrease in propulsive waves and total contractions 50 per cent greater than that obtained with placebos. These investigators found none of the synthetic antispasmodics tested equal in efficiency to the belladonna preparations. Pavatrine and Trasentin were among the commonly used antispasmodics tested.

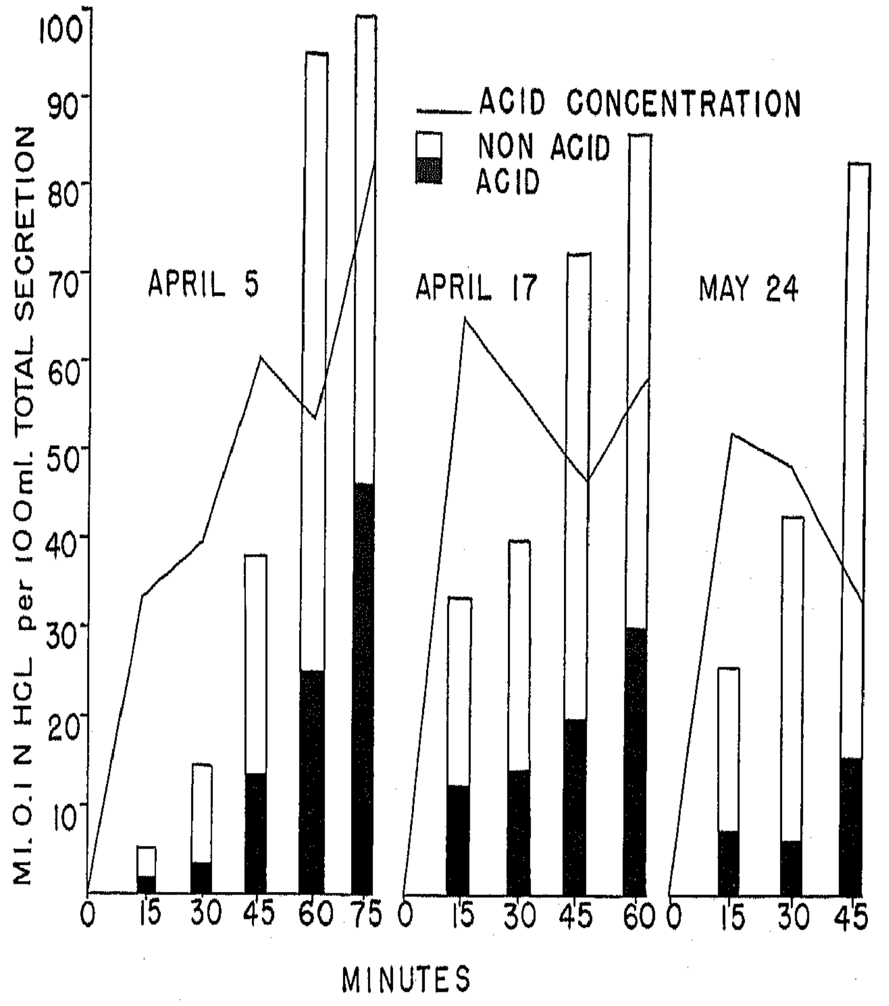


FIG. 37-3. The effect of therapeutic doses of atropine and simple general diet over a period of 50 days. This subject received $\frac{1}{100}$ grain of atropine sulfate orally, 4 times a day. The first analysis, on April 5, showed a typical duodenal ulcer curve; the high acid concentration resulted from secretion of a large amount of acid fluids. Analysis on May 24 showed a normal acid concentration and secretion of a larger volume of nonacid fluid. Emptying time and total gastric secretion decreased steadily throughout the experiment. (From W. D. Paul and C. Rhomberg, J. Iowa M. Soc., May, 1945.)

**Effect of atropine on the biliary duct.** Stimulation of the vagus nerve causes a contraction of the gall-bladder and relaxation of the sphincter of Oddi. Both atropine and scopolamine have been shown to reduce the secretion of bile and the synthesis of cholates in dogs with permanent fistulas of the gall-bladder (Skakun, 1958). Because of its anticholinergic activity atropine is useful in biliary colic with or without concretions in the gall-bladder. For this purpose atropine is frequently administered with meperidine.

**Effect of atropine on the eye.** When atropine is administered orally or parenterally in large doses, 3 to 6 mg., or when a diluted solution, 0.5 to 1 per cent, is instilled into the conjunctival sac, mydriasis and cycloplegia result. Figure 37-4 shows the innervation of the intrinsic muscles of the eye and the action of various drugs.

Atropine peripherally relaxes the sphincter muscle of the iris and the ciliary muscle. Each is innervated by one of the short ciliary nerves (cholinergic fibers). Thus it is observed that atropine in producing mydriasis combats the myosis evoked by physostigmine, pilocarpine, and other cholinergic drugs. By producing cycloplegia, atropine antagonizes the spasm of accommodation produced by the afore-mentioned cholinergic drugs.

The mydriasis produced by atropine is caused

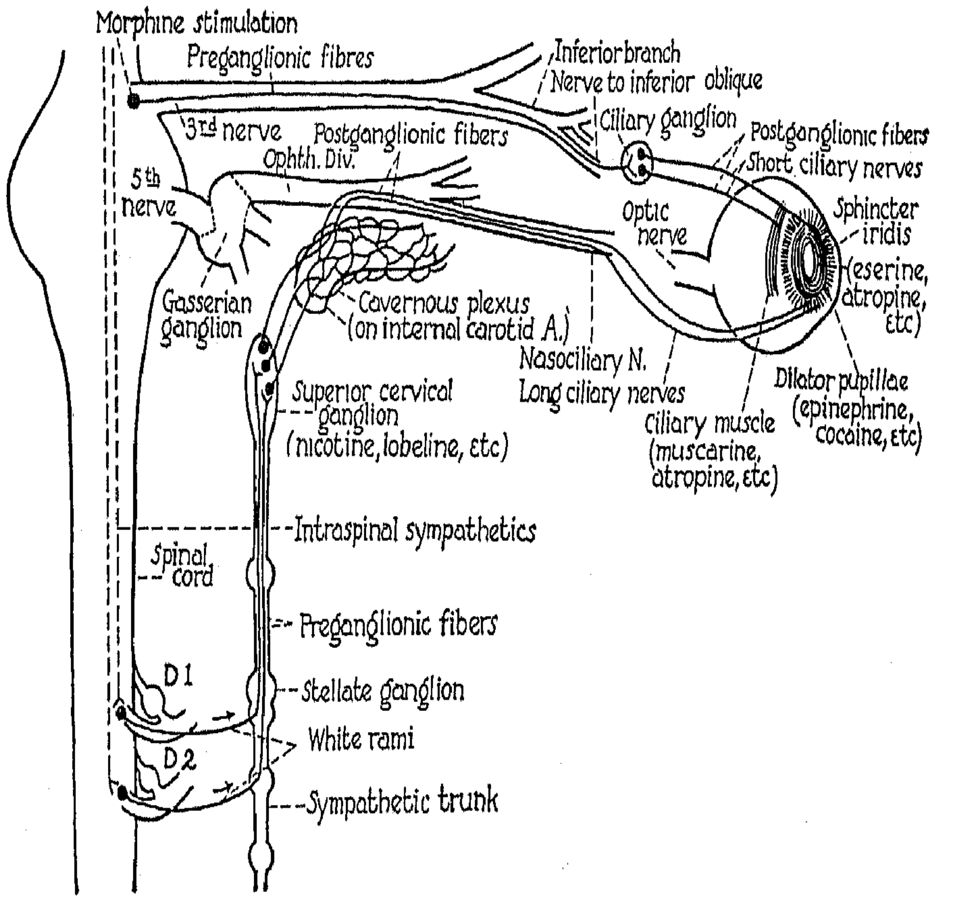


FIG. 37-4. Diagrammatic representation of the innervation of the intrinsic muscles of the eye. The sites of action of certain drugs which affect these muscles are also indicated. (From Jackson: *Experimental Pharmacology and Materia Medica*, C. V. Mosby Company, St Louis, 1939).

by the relaxation of the sphincter muscle of the iris. Atropine intervenes in the effector cells and blocks the action of acetylcholine. The radial muscle innervated by adrenergic fibers is then unopposed by the reciprocating action of the iris sphincter, and the pupil widely dilates. The dilatation which atropine evokes, therefore, is passive in character. When the radial muscle is simultaneously stimulated by the action of a sympathomimetic amine such as ephedrine, the pupil is further dilated. The mydriasis produced by atropine pushes the mass of the iris muscle against the cornea, blocking the cornea-iris angle where the drainage canal of Schlemm lies. This reduces the efficiency of drainage of ciliary fluid and gives rise to an increase in intraocular pressure, and atropine is hence interdicted in glaucoma.

When the ciliary muscle contracts at the junction of the choroid and the cornea, the choroid coat is pulled anteriorly. This lessens the tension on the suspensory ligament (zonule) and the lens extends forward by virtue of the elasticity of its anterior surface. Its anterior-posterior diameter is increased, and the lens is fixed for near vision (spasm of accommodation). When the ciliary muscle relaxes, such as after the action of atropine, the suspensory ligament is tightened. The lens becomes less convex, and the eye is fixed for distant vision (cycloplegia).

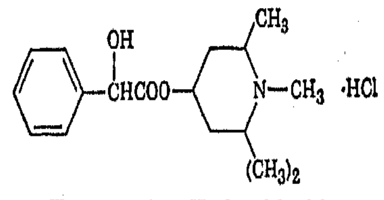
When a 1 per cent solution of atropine sulfate is dropped repeatedly into the conjunctival sac, the pupil begins to dilate in 10 to 20 minutes. A maximal effect is observed in 2 hours. The effect is unilateral at first, but later through absorption may become bilateral, and may last for 2 or 3 days. The cycloplegic effect of atropine begins in about 30 minutes after the administration of the drug. It lasts about 24 to 48 hours.

Although the use of atropine in the eye is useful in relieving pain in iritis and also in breaking adhesions between the iris and the cornea after certain surgical procedures, its principal use is in refraction. When used for this purpose, the drug widely dilates the pupil and thus provides for an ophthalmoscopic examination of the eye grounds. The cycloplegia makes it impossible for the individual to compensate for irregularities in the shape of the eye by straining the ciliary muscle. More adequate corrective lenses can be prescribed by refracting the normal and the cycloplegic eye. After 40 to 45 years of age the cycloplegic action is no longer necessary. The ciliary muscle, owing to a diminished tone, can no longer compensate for ocular defects, and the eye may be satisfactorily refracted without atropine.

For the purposes of refraction, *homatropine hydrobromide* is preferred to atropine sulfate. Its mydriatic and cycloplegic actions are prompt and less sustained than those of atropine. After refraction there is a shorter period of loss of accommodation. With homatropine the cycloplegia lasts about 12 hours and the mydriasis about 24 hours. A 2 per cent solution of homatropine hydrobromide is generally used. One drop is instilled in each eye every 15 minutes for 2 hours before refraction.

**Eucatropine Hydrochloride, U.S.P. (Euphthalmine).** This compound is a synthetic mydriatic drug. It is used to produce mydriasis for routine ophthalmoscopic examination of the eye grounds. Unlike atropine it does not produce cycloplegia and hence is not suitable for refractive purposes. The action is prompt (maximal dilatation in 30 minutes), and the duration is from 3 to 4 hours. Solutions of from 2 to 10 per cent are generally used.

The compound is a white, granular powder which is very soluble in water. The structure of eucatropine is shown in the formula below:



Eucatropine Hydrochloride
(1,2,2,6 tetramethyl-4-piperidyl
mandelate hydrochloride)

**Ocular drugs and the innervation of the iris.** The classical reciprocating innervations of the radial and sphincter muscles of the iris are shown in figure 37-4. The reciprocity of innervation is apparently more complicated when studied critically by means of various drugs. Joseph (1916) showed that epinephrine relaxed the isolated sphincter of the steer's iris, indicating the presence of sphincter muscle inhibitory elements which are adrenergic in character. The same author demonstrated sphincter inhibitory elements in the cervical sympathetic nerve of the anesthetized cat.

Yonkman (1934) injected cats with ergotamine (which paralyzes the motor sympathetics in the radial muscle of the iris) and atropine intraocularly. He then subjected the cervical sympathetic nerve to faradic stimulation. The pupil dilated upon faradic stimulation. Yonkman states:

> "Because these data confirm Joseph and the results obtained from our studies on the isolated iris sphincter of the steer and dog eye, the author is inclined to believe that pupillary dilatation produced by the various sympathomimetics—cocaine, ephedrine, and adrenalin—may be explained not only on the basis of stimulation of sympathetic motor effector cells in the radial musculature but also by simultaneous stimulation of sympathetic inhibitory effector cells in the circular muscle fibers of the iris sphincter."

Olmsted and Morgan (1939) produced evidence to show also that the ciliary muscle of the rabbit contains sympathetic inhibitory elements which synergize the activity of homatropine.

**Action of atropine on sweat and salivary excretion.** Atropine is a prompt and dependable drug to check the excretion of sweat and saliva. The administration of as little as 0.6 mg. of atropine will reduce the sweat excreted to ½ or ⅓ its normal amount. The action comes on in about ½ hour and persists for 3 or 4 hours. This action is mediated through the blocking of acetylcholine in the effector cells of the sweat glands by atropine. This *anhidrotic* action of atropine has been employed clinically to check the night sweats of tuberculosis. The anhidrotic action of atropine is effectively combated by the diaphoretic action of pilocarpine or neostigmine.

If the chorda tympani of an animal is stimulated, a copious flow of limpid saliva, low in organic solids, results. Upon the injection of atropine the action is terminated. The action is peripheral to the ganglion and is therefore not blocked by nicotine. It results from the action of atropine in its interference with acetylcholine action at the hilus of the submaxillary gland. A drug producing salivation, such as pilocarpine, is called a *sialogogue*. One which decreases salivary flow, such as atropine, is termed an *anhidrotic*, which is a more general term and applies to the secretion of sweat as well as saliva.

When the adrenergic effector cells in the salivary glands are stimulated by excitement (endogenous epinephrine) or by the injection of epinephrine, salivation also results. This type of saliva is viscid, rich in organic solids (about 6 per cent), and possesses little lubricating property for the buccal membranes. It gives one the sensation of dry mouth (xerostomia) and is characteristic of states of anxiety and sudden fear.

**Action of atropine on sensory nerve end-**

**ings.** When preparations containing belladonna extracts or atropine are applied locally to the skin, sensory perception in the area is partially blocked. The action is most marked if the preparation is prepared as an ointment or liniment. The action of atropine upon sensory nerve endings is more pronounced if the ointment or liniment is applied to a local lesion, such as a rectal fissure or hemorrhoids. For this purpose belladonna ointment, which contains 10 per cent of extract of belladonna and represents 40 per cent of belladonna leaves, has enjoyed widespread use for years. Belladonna suppositories containing 0.1 gm. of belladonna extract are useful as an *anodyne* in the treatment of painful hemorrhoids. The suppository is also of value in relieving the pain of cystitis and prostatitis, which is often referred to the perianal region.

Prolonged application of belladonna preparations to the skin may result in systemic belladonna poisoning. This is particularly a possibility when the belladonna liniment is applied to large areas of the skin with inunction. Pupillary dilatation produced by the local application of a belladonna preparation to the skin should be considered as a premonitory symptom of systemic belladonna poisoning.

**Effect of atropine on body temperature.** After a large therapeutic dose of atropine (1 mg.), an increase in body temperature of 1 or 2°F usually occurs. This effect of atropine is probably the result of its anhidrotic action. It diminishes the sweat secretion and the heat loss which accompanies the evaporation of water from the surface of the skin. This rise in temperature occurs in spite of the cutaneous vasodilatation produced by the drug. In the dog, which does not possess sweat glands, atropine does not produce hyperpyrexia. In severe cases of atropine poisoning the body temperature might rise to 104 or 105°F.

**Other pharmacologic responses of atropine.** Atropine is of value in renal colic. The drug blocks the action of acetylcholine in the effector cells of the ureters and thus produces relaxation. It may allow the passage of calculi through the ureters. Atropine is valuable also in these conditions to depress vagal activity and thus obliterate the possibility of a cardiac reflex action. The atropine dosage in these conditions is 1 mg. subcutaneously combined with 15 mg. of morphine.

Atropine is indicated in incontinence of urine resulting from excessive vagus tone. The cholinergic fibers are motor to the wall of the bladder and relaxant to the sphincter muscle. Atropine intervenes and causes a relaxation of the bladder wall and an increased tonus of the vesical sphincter. Charvát and Holeček (1956) observed that the administration of 0.5 mg. of atropine prevented the release of the antidiuretic hormone (ADH) in individuals who have previously received intravenous injections of hypertonic saline solution.

Atropine is relaxant to the nongravid human uterus. It has been used with some degree of success in the treatment of dysmenorrhea caused by uterine hypertonicity.

Although the usual therapeutic doses of atropine block the action of acetylcholine in smooth muscle, under experimental conditions it has been established that larger doses injected intra-arterially will inhibit the response of voluntary muscle to nerve stimulation. Tum-Suden (1958) demonstrated that 1 to 2 mg./kg. of atropine would inhibit the contraction of the tibialis anticus muscle of the cat, dog, and monkey to the extent of 50 to 100 per cent. The effect is transient; however, residual amounts of atropine in the muscle produce an inhibition to the response to acetylcholine for a period of 30 minutes after the apparent recovery of the muscle to nerve stimulation.

**Fate of atropine in the body.** Atropine disappears rapidly from the blood and about 50 per cent is excreted undecomposed in the urine in man (Gosselin *et al.*, 1960). The fate of atropine in the animal body enjoys a wide species variation. The rabbit is capable of decomposing large quantities of atropine by virtue of a special enzyme contained in the liver. Ellis (1947) found that there was a great variation among individual rabbits with regard to the capacity of their plasmas, livers, and kidneys to degradate atropine. In general, Ellis found that the viscera of rabbits, which possess a great capacity to hydrolyze benzoylcholine, also are capable of hydrolyzing large quantities of atropine. In other words, rabbit livers have large quantities of both atropine esterase and benzoylcholinesterase, or small quantities of each. In other species the concentrations of the two esterases did not parallel each other.

Rabbits can eat belladonna leaves *ad libitum* with impunity. Death of an entire family poisoned by the eating of a rabbit which had ingested belladonna has been reported.

The excretion of atropine unchanged in the urine of man is a faithful criterion of atropine administration. A drop of the suspected urine, when instilled into the conjunctival sac of a cat, will produce mydriasis. An amount as small as 0.2 μg. of atropine will produce mydriasis.

Gabourel and Gosselin (1958) studied the fate of atropine in the mouse and rat using $C^{14}$-labeled atropine in the alpha position of the tropic acid portion of the molecule. Approximately 25 per cent of the injected atropine appeared in the urine unchanged; more than 50 per cent was present as glucuronides and the remainder as products of degradation. The liver was the site of glucuronide formation.

**Toxicology of atropine.** The symptoms which usually are evoked by various dosage levels of atropine are listed in table 37-1.

Atropine and morphine are frequently given simultaneously; it is well to remember that the therapeutic dose of morphine, 10 mg., is a toxic and possibly a fatal quantity of atropine.

Atropine poisoning often results from errors made in the handling of atropine prescriptions by unskilled technicians who are not aware of its potentialities for harm.

The symptoms of intoxication set in promptly after a toxic dose. As a rule they persist for a long period of time, and the physician is able to use combative measures to save the patient's life. The following are the classic symptoms of atropine poisoning:

1. Severe dryness of the throat and mouth
2. Wide dilatation of the pupils and loss of accommodation
3. Dysphagia and thirst
4. Tachycardia
5. Redness of skin in blush area with marked dryness
6. Muscular incoordination, marked weakness
7. Rise in body temperature
8. Hallucinations or even mania
9. Apathy and unconsciousness
10. Stertorous breathing—depressed respiration, and finally, respiratory collapse

In the treatment of atropine poisoning pilocarpine, physostigmine, and morphine have all had their use as physiologic antidotes. The drug of choice today is neostigmine methylsulfate. Parenterally 0.5 to 1 mg. may be administered, repeated every 2 or 3 hours. As the patient improves, 15 mg. of neostigmine bromide may be used orally in place of the parenteral medication. The delirium may be treated by the application of an ice cap to the head. Artificial respiration should be instituted if required. Respiratory stimulants such as caffeine and sodium benzoate and oxygen-carbon dioxide mixtures may be indicated.

TABLE 37-1

*Atropine Symptomatology*

| Mg. | Symptoms |
|---|---|
| 0.5 | Slowing of pulse, some throat dryness |
| 0.5–1 | Xerostomia, often thirst |
| 2 | Mydriasis, pupil not quite immobile, quickened pulse |
| 3–5 | Headache, dysphagia, malaise, muscular weakness |
| 7 | Wide mydriasis, visual disturbance |
| 8 | Excitation, marked muscular incoordination |
| 10 | Apathy, hallucinations or delirium, unconsciousness |

In the usual therapeutic doses atropine may be taken for years by many patients, especially those with gastrointestinal symptoms, without untoward symptoms or the development of tolerance.

**Therapeutic uses of atropine.** The therapeutic uses of atropine are numerous, and many have been discussed in the foregoing paragraphs. The principal therapeutic uses are summarized in the following statements.

1. Atropine is used to relieve the *spasm of smooth muscle.* For this purpose it is valuable in the treatment of *gastric hypermotility, spasticity of the small intestine and colon*, and *pylorospasm.* Because it diminishes the gastric secretion of acid, it is indicated routinely in the treatment of *peptic ulcer.*

As an antispasmodic, atropine is used in *bronchial asthma.*

Atropine is also valuable for relaxing the *spasticity of the ureter and bile ducts* when concretions are absent or present. The antispasmodic action of atropine has warranted its use in the treatment of *dysmenorrhea.*

2. Atropine and its companion drug homatropine are useful in the production of *mydriasis* and *cycloplegia* for the refraction of the eye for lenses. Homatropine, for reasons stated previously, is the drug of choice.

Solutions of atropine sulfate 0.5 to 1 per cent are used locally to relieve the pain of *corneal ulcers.* Atropine is used also in *iritis* and to prevent the formation of *adhesions* between the iris and the cornea. For the latter purpose it is used alternately with physostigmine solutions.

3. Atropine is used in *urinary incontinence* caused by hypertonicity of the parasympathetic nerves to the bladder wall and sphincter.

4. As an anhidrotic, atropine may be used in checking perspiration.

It is used to diminish *salivary* and *bronchial secretions during anesthesia.* When atropine or scopolamine is used parenterally as preanesthetic medication for nonocular surgery in patients with glaucoma, either pilocarpine or physostigmine solution should be instilled into the conjunctival sac to evoke myosis. This procedure counteracts the potential mydriatic effect of atropine or scopolamine (Schwartz *et al.*, 1957).

Atropine is often employed in the treatment of *grippal conditions* when these are accompanied by excessive *nasal secretion.*

5. Belladonna and its preparations are used in *parkinsonism.* For this purpose stramonium tincture, belladonna tincture, scopolamine, mixtures of belladonna alkaloids, and atropine alone have been used.

6. Atropine is used in the treatment of *heart block* (see page 662).

### Scopolamine (Hyoscine)

**Scopolamine Hydrobromide, U.S.P.** Scopolamine hydrobromide occurs as colorless or white crystals or as a white granular powder. The salt crystallizes with water and is efflorescent in dry air. One gm. of the compound dissolves in 1.5 ml. of water. The chemical constitution of scopolamine has been given on page 598. The U. S. Pharmacopeia recognizes only optically active scopolamine, *i.e.*, the levo compound. The optically inactive compound known as *atroscine* exhibits a much weaker pharmacologic activity.

**Anticholinergic action of scopolamine.** Like atropine, the alkaloid scopolamine acts upon the effector cells in the viscera innervated by cholinergic nerves. Here it blocks the action of acetylcholine and hence depresses cholinergic activity. The anticholinergic activities of the two compounds parallel each other. There are, however, certain quantitative differences between the actions of the two alkaloids on different structures. For example, scopolamine is a more powerful mydriatic and cycloplegic. It is also a more potent anhidrotic. But on the cardiac vagus, atropine is more potent than scopolamine.

**Response of the cerebrum to scopolamine.** The principal difference in the responses evoked by atropine and scopolamine is the cerebral action. In ordinary therapeutic doses atropine elicits no response on the brain. In larger doses the primary action of the drug is excitant in character. Scopolamine, on the other hand, is primarily a cerebral depressant in all therapeutic doses.

The action of scopolamine on the brain in man comes on promptly after a subcutaneous injection of 1 to 3 mg. The individual feels drowsy and apathetic and sleep ensues and lasts for several hours. This response, however, is not constant in all persons, for often the depressed psychic state is preceded by a period of excitation, hallucinations, and disorientation.

Ostfeld and Aruquete (1962) administered scopolamine subcutaneously in doses of 0.15 to 0.8 mg. to 54 subjects and studied the effects on salivary flow, EEG, motor behavior, mood, and ability to focus and maintain attention. The drug evoked bradycardia, decrease in salivation, and decrease in the duration of the EEG arousal response to photostimulation. Higher dosage levels were associated with a decrease in performance on behavioral tests involving the capacity to maintain attention. This recent study, involving modern psychological technics, confirms years of clinical observations on the action of scopolamine.

**Therapeutic uses of scopolamine.** Scopolamine is used principally to produce its sedative effect on the cerebrum. It is frequently given with morphine. It is believed that scopolamine potentiates the action of morphine on the brain. Although the evidence for potentiation is not entirely convincing, it is undoubtedly true that there exists a synergism between morphine and scopolamine (Smith, 1915).

1. Scopolamine is used with morphine or a barbiturate for *preanesthetic medication.* It appears that the scopolamine-barbiturate combination is preferred by many anesthesiologists to the scopolamine-morphine medication. Gauss (1906) suggested the use of moderate doses of morphine in combination with large doses of scopolamine in the production of *scopolamine-morphine amnesia, "twilight sleep."* The drug combination produces a blurred consciousness in which pain is not completely obtunded but made less poignant. The memory of the patient is impaired in reproducing the events in consciousness which occurred during the twilight sleep. For many years this combination of drugs enjoyed wide use in obstetrics. The drugs today are being replaced by other agents. The principal difficulty encountered in scopolamine-morphine amnesia is the variability of response. Some patients, as previously suggested, become delirious or even maniacal under its action prior to the onset of the sedative effect.

For the purpose of producing amnesia, 15 mg. of morphine is injected with 0.5 mg. scopolamine. The morphine dosage is not repeated, but the scopolamine may be repeated in 45 to 60 minutes and in 1½ hours after the second dose.

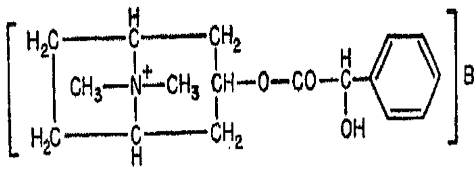
2. Scopolamine has been used successfully in sedating patients with *delirium tremens.* It is also used in terminating *acute maniacal states.* In each instance the drug is administered subcutaneously in doses of 0.6 to 0.8 mg. The effect is prompt and lasts for several hours.

3. The use of scopolamine in motion sickness is discussed in Chapter 30.

### Atropine Congeners

In recent years many synthetic compounds related to atropine have been made available as therapeutic agents. Many of these exhibit advantages over atropine in special types of therapy. In order to retain the atropine-like action, the ester is generally derived from an acid possessing an asymmetric carbon atom, such as tropic or mandelic acid. Most of these drugs are employed as antispasmodics, *i.e.*, they diminish or abolish the spasms of smooth muscle. They are also referred to as *spasmolytics.* The synthetic antispasmodics of the atropine group are used extensively to relieve gastrointestinal irritability, pylorospasm, gastric hypermotility, and dysmenorrhea owing to uterine hypertonicity. They are also used in the treatment of hyperirritable states of the urinary bladder. In certain individuals atropine, when given in sufficient dosage to produce its spasmolytic effect, may produce tachycardia, xerostomia, and visual disturbances.

**Homatropine Methylbromide, U.S.P.** This derivative of homatropine is a white, crystalline powder. It is readily soluble in water and alcohol. The structure of homatropine methylbromide may be observed from the formula:



Homatropine Methylbromide, U.S.P.
Camatropine, Mesopin, Novatropine

It will be observed from the foregoing formula that homatropine methylbromide is homatropine in which the nitrogen atom of the tropanol nucleus has been quaternized.

Homatropine methylbromide is used mainly as a spasmolytic agent in the treatment of gastrointestinal spasm. It is about ½ as potent as atropine on the gastrointestinal tract, but it is claimed to be only 1/30 as toxic. Its use in gastrointestinal hypermotility is generally accompanied by fewer untoward side actions than is atropine. Therapeutically effective doses seldom produce visual disturbances, xerostomia, or tachycardia.

Homatropine methylbromide is used in the treatment of peptic ulcer, pylorospasm, hyperchlorhydria, and spasticity of the colon.

It is usually given orally in tablets of 2.5 mg. 2 to 3 times daily prior to meals. The adult dose is 1 to 2 tablets. The drug may also be administered subcutaneously or intramuscularly for acute spastic conditions. The recommended parenteral dose is 5 mg. Our observations and the reports of the use of this drug coming to our attention are favorable, and it appears to warrant a definite place as a spasmolytic.

**Epoxymethamine Bromide (Pamine Bromide).** Pamine bromide is an anticholinergic drug related to atropine. It is the methylbromide of epoxytropine tropate. Its action and uses are similar to those of atropine and homatropine methylbromide. The principal conditions in which Pamine is used are peptic ulcer and gastric disorders associated with hyperacidity and hypermotility.

The capacity of Pamine to diminish gastric secretion was shown by Kirsner and Palmer (1953). The administration of 5 to 25 mg. of Pamine orally produced anacidity in about half of their patients. Xerostomia was comparatively mild. Chapman *et al.* (1955) studied the effect of Pamine, methantheline, and placebos on gastrointestinal motility in man when fasted and after a standard test meal. Pamine and methantheline produced significantly more delaying action on intestinal motility, as compared with placebos, during the period of fast than after the test meal. The meal reduced the intestinal relaxant action of methantheline more than that of Pamine. The drugs were compared at a dosage level of 5 mg. of Pamine and 50 mg. of methantheline. In these dosages gastric emptying time was not significantly affected.

The dose of Pamine is 1 tablet (2.5 mg.) $\frac{1}{2}$ hour before meals and 2 tablets at bedtime. The drug is a dependable anticholinergic agent.

**Amprotropin (Syntropan).** Syntropan occurs as a white, crystalline powder with a faint roseate odor. It is freely soluble in alcohol. The chemical constitution of Syntropan is given on page 598. Fromherz (1937) studied the pharmacologic responses to Syntropan and compared them with atropine. Among his findings which are of clinical interest are the following:

1. The mydriatic action of Syntropan on the cat's eye is about $\frac{1}{100}$ that of atropine. Besides, the action of Syntropan is more evanescent.
2. The action of Syntropan in depressing the sialogogue response of pilocarpine in the rabbit is $\frac{1}{100}$ that of atropine.
3. The anticholinergic activity of Syntropan as measured by its action on the blood pressure of the cat is $\frac{1}{500}$ that of atropine.
4. The spasmolytic action of Syntropan, however, as shown on the isolated rabbit's intestine, is $\frac{1}{20}$ that of atropine. The spasmolytic action appears to be musculotropic as well as acting through the cholinergic innervation.

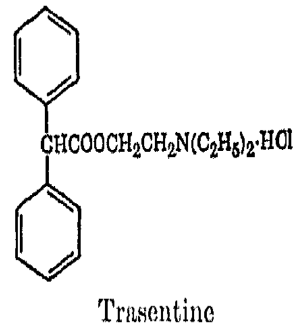
Clinically the experimental observations of Fromherz have been demonstrated with Syntropan as a spasmolytic. Syntropan appears to be a useful and dependable antispasmodic, particularly in peptic ulcer and associated pylorospasm.

Syntropan is available in 50-mg. tablets for oral administration; 1 tablet is given prior to meals and at bedtime. The drug may also be used parenterally (subcutaneous or intramuscular) in doses of 10 mg. in 1 ml. of solution.

**Adiphenine (Trasentine).** Trasentine occurs as white, crystalline needles which are stable in the air and readily soluble in water. The chemical constitution of Trasentine may be observed from the accompanying formula.

Trasentine is useful as a spasmolytic in the treatment of gastrointestinal hypermotility. It is widely used in the treatment of peptic ulcer. In addition to the spasmolytic action of Trasentine, the drug evokes a mild local anesthetic action.

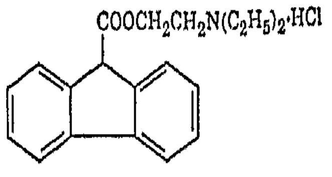
Trasentine is available in tablets of 75 mg. each.



Trasentine
(2-diethylaminoethyldiphenylacetate hydrochloride)

The dose is 1 to 2 tablets before meals and at bedtime. The drug is available also for intramuscular use in doses of 50 mg. and for rectal administration in 100-mg. suppositories.

**Pavatrine.** Pavatrine occurs as a white, crystalline powder. It is soluble in water. The chemical constitution of Pavatrine may be observed from the accompanying formula.

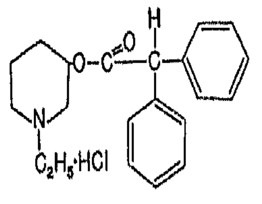


Pavatrine
(β-diethylaminoethyl fluorene-9-carboxylate hydrochloride)

Pavatrine is a typical spasmolytic which evokes neurotropic and musculotropic relaxation of smooth muscle. It is recommended for use in the same class of spastic conditions of smooth muscle as is atropine and Syntropan.

Pavatrine is available in tablets of 125 mg. each. The dosage schedule is 1 to 2 tablets prior to meals and at bedtime.

**Piperidolate Hydrochloride (Dactil).** Dactil is an agent useful by virtue of its anticholinergic action. Like Piptal it is a piperidyl derivative, as shown in the formula:



Dactil
(N-ethyl-3-piperidyl diphenylacetate hydrochloride)

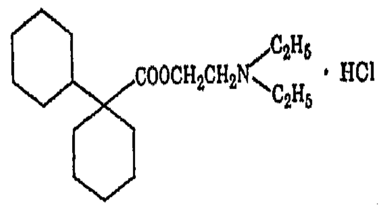
Dactil is a white, crystalline powder which is readily soluble in water.

Dactil is used mainly to diminish spasm of the duodenum and biliary tract. It relaxes the sphincter of Oddi and the duodenum more than does

papaverine; its relaxant action is comparable to that elicited by Trasentine (Chen and Beckman, 1952). In therapy Dactil is used mainly in the treatment of *pylorospasm*, *cardiospasm*, and *biliary dyskinesia*. Although Dactil is useful in duodenal hypermotility, it does not inhibit the gastric secretion of acid. Dactil therapy is not fraught with the xerostomia or visual disturbances which so frequently accompany many of the anticholinergic drugs.

Dactil is available in 50-mg. capsules. The usual daily dose is 4 capsules.

**Bentyl Hydrochloride (Dicyclonine).** This compound is an antispasmodic to smooth muscle. Chemically it is diethylaminocarbethoxybicyclohexyl hydrochloride, as shown in the formula below.



Bentyl Hydrochloride
(2-diethylaminoethyl bicyclohexyl-1-carboxylate hydrochloride)

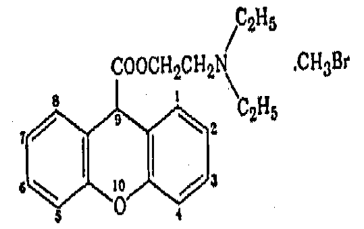
On the isolated intestinal strip Bentyl exhibits $\frac{1}{6}$ the activity of atropine against the acetylcholine-induced spasm. Bentyl retards the passage of a charcoal meal through the intestines of the rat. The mydriatic and antisialogogue actions of Bentyl are approximately $\frac{1}{400}$ and $\frac{1}{300}$ of those of atropine (Brown *et al.*, 1950). Bentyl is metabolized for the most part in the body. Only 15 per cent is excreted in the urine.

Bentyl has been found to be useful clinically in the treatment of functional digestive diseases and dysmenorrhea. Chamberlin (1951) found the compound effective as an antispasmodic and quite free from undesirable side effects.

The absence of adverse side effects with Bentyl therapy was observed by McHardy and Browne (1952) in a comprehensive comparative study with various antispasmodics. They employed barium motility studies in hyperperistaltic patients, fluoroscopic evaluation of effects on pylorospasm, and the symptomatic relief of the patients as criteria. They found Bentyl, Prantal, and methantheline to exhibit comparable degrees of efficacy as antispasmodics. Each of the three drugs was found to be superior to atropine in their studies on upper gastrointestinal tract dysfunction. Prantal and methantheline evoked greater degrees of antisecretory action than did Bentyl. They state: "The freedom from significant side effects with Bentyl permits more general use when secretory inhibition is not of first import."

The use of anticholinergic drugs in patients predisposed to or having glaucoma presents a difficult therapeutic problem, since most of the anitcholinergic drugs aggravate the condition. Cholst *et al.* (1958) studied the effects of Bentyl in 37 patients who were normal with respect to ocular disease and in 17 patients with chronic simple glaucoma. They observed that Bentyl did not significantly increase the intraocular pressure or affect the pupil size or accommodation of the eye. The dose is 10 to 20 mg. 3 times a day.

**Methantheline Bromide, N.F. (Banthine).** The use of atropine and atropine-like substances in the treatment of gastric hypermotility and peptic ulcer has prompted a continuous search for more effective substances in this field of therapy. Grossman (1950), commenting on a more effective agent in this type of therapy, said: "What is being sought is essentially a cholinergic blocking agent with specificity for site of action." It appears that the synthesis of methantheline offers a more interesting molecule for this field of study. The essential pharmacologic responses of methantheline are autonomic ganglion blocking and atropine-like action. The structure of methantheline is shown in the accompanying formula.



Methantheline Bromide, N.F.
Banthine
(β-diethylaminoethyl xanthene-9-carboxylate methobromide)

Grimson (1949) demonstrated that methantheline was capable of blocking the stimulating effects of acetylcholine on the rabbit's ileum. It appears to be about 0.7 as effective as atropine. The depressor response elicited by vagus stimulation is blocked by methantheline, and further, the compound was shown to produce mydriasis and check salivation.

The quaternary amine structure of methantheline suggests autonomic ganglion blocking. This action was demonstrated by stimulating the preganglionic fiber of the cervical sympathetic nerve in the cat. After methantheline the nicitating membrane failed to respond to stimuli applied to the preganglionic fibers. Other experiments indicated that the drug blocked both parasympathetic and sympathetic ganglia simultaneously. Thus methantheline exhibits activity on two facets of the parasympathetic system, namely, ganglionic and cholinergic blockade. On the sympathetic system its action is restricted to the ganglion.

In larger doses methantheline was shown to produce a curare-like action on skeletal muscle. This effect was obliterated by the administration of neostigmine.

Specific ganglionic blockade in the autonomic nervous system is likely not to be achieved by anticholinergic agents of the methantheline type in the usual therapeutic dose. It has been estimated that a 40-fold increase in dosage level is required for sympathetic blockade. Further failure to block the gastric acid secretion concomitant to the injection of insulin, which is blocked by the ganglionic blocking agent hexamethonium, suggests an activity which is mainly anticholinergic. After a comprehensive pharmacologic investigation of this ganglionic blockade with methantheline and propantheline, Johnson and Wood (1954) state: "It seems, therefore, that ganglionic blockade is not likely to be responsible for any therapeutic effects when these substances are used clinically unless a dosage range is used which would produce pronounced signs of peripheral parasympathetic blockade."

The effectiveness of methantheline as a gastrointestinal antispasmodic was studied extensively in man. When administered orally in 100-mg. doses, methantheline was shown to diminish significantly gastric motility, gastric secretion, intestinal motility, and colonic motility. The activity of the drug was compared with 0.45 mg. of atropine sulfate and found to exhibit a greater degree of gastrointestinal relaxation.

Longino *et al.* (1950) employed methantheline in the treatment of peptic ulcer. They were impressed by the capacity of the compound to relieve promptly pain produced by peptic ulcers. Grimson *et al.* (1950) used methantheline in ulcer patients; of these, most stated that pain had completely abated, and the remaining patients suffered only mild and infrequent pain. These findings have been confirmed in other clinics on many ulcer patients (McHardy *et al.*, 1951). The value of methantheline as a dependable spasmolytic can be considered established. However, the drug should not be considered a substitute for conventional ulcer therapy, but rather as an adjunct to it.

The dosage of methantheline is 50 to 100 mg. every 6 hours, including nocturnal medication. The untoward effects of methantheline appear to be few. Grimson observed mydriasis and xerostomia of mild degree in some patients. In elderly patients with prostatic hypertrophy, some urinary retention may develop because of the powerful atropine-like action of methantheline. Delayed gastric emptying may occur in the early stages of therapy, but the condition appears to be of short duration.

Extensive investigations in man have laid a basis for the success of methantheline in ulcer therapy. Using multiple balloon kymograph recordings of the gastrointestinal tract, Chapman *et al.* (1952) found methantheline to be superior to belladonna tincture as a spasmolytic. Indeed 0.4 ml. of the tincture diminished the contractions only slightly more than a placebo. Xerostomia was more marked with methantheline, however, than with belladonna. Tachycardia was also produced by methantheline. Texter *et al.* (1952), in studying the mechanism of pain relief by methantheline, concluded that this was achieved mainly by blockade by the parasympathetic motor innervation of the stomach and duodenum.

*Other uses of methantheline.* Methantheline has been used successfully in relieving excessive sweating. It appears that the side effects of the drug are not too serious nor too frequently encountered. However, Clarke and McNaughton (1952) reported a case of exfoliative dermatitis as the result of methantheline therapy.

Methantheline has had considerable use as an anticholinergic agent in urology. It is valuable in relieving enuresis of neurogenic origin or that associated with hemiparesis or multiple sclerosis.

Howard *et al.* (1952) observed that methantheline markedly reduced the volume of pancreatic secretion.

Methantheline has been used in place of atropine to check salivation prior to anesthesia. The drug is very effective for this purpose.

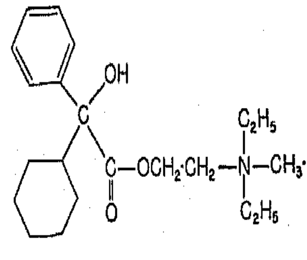
**Propantheline Bromide U.S.P. (Pro-Banthine Bromide).** Propantheline is a more potent cholinergic blocking agent than methantheline. It also elicits autonomic ganglionic blockade. The chief advantages of propantheline over methantheline appear to be that it is 2 to 5 times more potent than methantheline, and that the incidence of untoward reactions is less. Structurally the two compounds differ in that propantheline contains 2 isopropyl groups attached to the quaternary nitrogen atom instead of the 2 ethyl groups present in methantheline. The indications for the two drugs are the same.

The recommended dosage schedule of propantheline is 15 mg. (1 tablet) with meals and 30 mg. at bedtime. Like methantheline, propantheline may be administered parenterally. The dose of propantheline intramuscularly or intravenously is 30 mg., while that of methantheline is 50 mg. Reports of the clinical use of propantheline are equally as favorable as those with methantheline, and the regimen is apparently fraught with fewer disturbing side reactions.

Barowsky *et al.* (1955) employed propantheline in the treatment of a series of peptic ulcer cases, using double the recommended dose to achieve a more complete cholinergic blockade. Gastric inactivity was induced, and the pylorus was relaxed. The incidence of good responses increased from 76 to 92 per cent with increased dosage. No serious toxic effects or side reactions were observed as a result of the larger dosage schedule. Their dosage ranged from 270 to 330 mg. daily instead of the conventional schedule of 60 to 120 mg. Perhaps under-medication has been the cause of the failure with propantheline in some cases.

Like most of the anticholinergic drugs, propantheline is often prescribed with phenobarbital where tension appears to be a salient factor in the gastrointestinal dysfunction. In more recent years one of the tranquilizing drugs is frequently used in place of phenobarbital. Thus propantheline is available in 15-mg. tablets containing 5 mg. of Dartal (see page 506), a phenothiazine tranquilizing agent.

**Oxyphenonium Bromide (Antrenyl).** This substance is an anticholinergic agent which, like methantheline, also exhibits ganglionic blocking activity. Chemically it is diethyl-(2-hydroxyethyl)-methylammonium bromide 2-phenyl-cyclohexaneglycolate, as shown in the formula below.



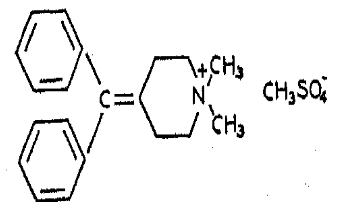
Oxyphenonium Bromide
Antrenyl

The compound is a white, crystalline powder which is readily soluble in water.

Antrenyl, through its anticholinergic activity and ganglionic blocking action, has been shown to relax the spasm of smooth muscle of the intestine. It appears to be as potent as atropine and more lasting in its effect. The antisialogogue effect of Antrenyl is less marked than that of atropine. It markedly depresses the secretory activity of the parietal cells of the stomach.

Antrenyl is indicated in the treatment of peptic ulcer and spasms of the gastrointestinal tract. Rogers and Gray (1952) found Antrenyl to be an effective drug in peptic ulcer. It relieved the symptoms promptly, diminished acid secretion, and was well tolerated. Antrenyl is given in tablets of 5 mg., 4 times a day. The dosage may be increased to 12.5 mg., 4 times a day, until the desired relief is achieved. The common untoward side effects are *xerostomia, blurring of vision,* and *constipation.*

**Diphemanil Methylsulfate (Prantal Methylsulfate).** This compound is another anticholinergic agent with ganglionic blocking activity similar to that of methantheline and Antrenyl. Chemically it is N,N-dimethyl-4-piperidylidene-1-diphenylmethylene methylsulfate, as shown in the formula below:



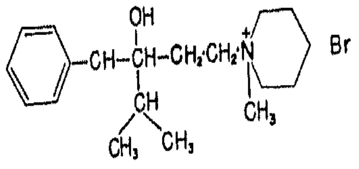
Diphemanil Methylsulfate
Prantal Methylsulfate

It is a crystalline powder, readily soluble in water.

Prantal is reported to be more active than methantheline as a spasmolytic on the gastrointestinal tract. It does not produce mydriasis to any appreciable extent. Rowe *et al.* (1952) employed the drug in a series of patients and observed that intramuscularly the compound was equal to methantheline. Orally they observed that the reduction of intragastric pressure was not as consistent or as prolonged as that achieved with methantheline. The dosage schedule orally is 50 to 200 mg. (½ to 2 tablets) every 4 to 6 hours. Rowe *et al.* noted distinct improvement in only half of his series of patients.

Marks (1952) found Prantal effective in 89 per cent of a series of 46 ulcer patients. Side effects were minimal. Of interest is the extensive study of McHardy and Browne (1952) on the comparative value of antispasmodics. They found Prantal, methantheline, and Bentyl to be equally efficacious. Each of the three drugs appeared to be superior to atropine.

**Mepiperphenidol Bromide (Darstine).** This anticholinergic agent contains a quaternary nitrogen atom, as shown in the formula:



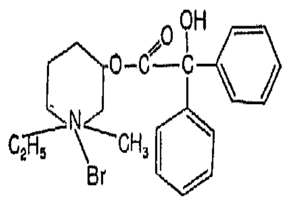
Darstine
[1-(3-hydroxy-5-methyl-4-phenylhexyl)-1-methylpiperidinium bromide]

Darstine is a white, crystalline powder which is soluble in water.

The anticholinergic activity of Darstine is less than that of atropine, but comparable to that of methantheline. Darstine was found to exert specificity for the cholinergic structures of the gastrointestinal tract, and in doses in which it inhibited gastrointestinal motility, it produced little effect upon salivary excretion. McCarthy *et al.* (1953) observed that Darstine exerted an inhibitory action on the denervated gastric pouch. Darstine appears to be excreted in the urine as such during a period of 48 to 72 hours after its administration.

Clinically, Darstine is used like other anticholinergic drugs. In the control of gastric secretion and gastrointestinal hypermotility Sun *et al.* (1955) found Darstine effective in daily doses of 50 to 400 mg. Like methantheline, it also has been used successfully in hyperhidrosis.

**Pipenzolate Methylbromide (Piptal).** This substance is an anticholinergic agent containing a quaternary nitrogen atom, as shown in the formula:



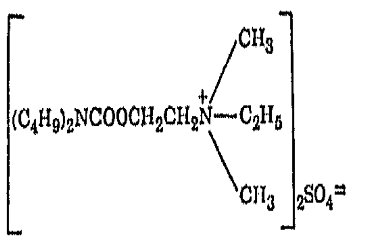
Piptal
(N-ethyl-3-piperidyl benzilate methobromide)

Piptal occurs as a white, crystalline powder which is freely soluble in water.

Cholinergic blocking by Piptal is comparable to that evoked by atropine. Riese (1955) studied Piptal in human subjects and found that in most cases it diminished gastric acidity. A dose of 15 mg. reduced gastrointestinal motility and relieved spasm, as shown by x-ray observations. His studies showed the drug to be effective in the treatment of peptic ulcer, with a minimum of side effects. Klotz (1956) found Piptal effective as a potent antisecretory agent in 88 patients. Piptal has been found to be effective in the treatment of colic of early infancy. The pediatric Piptal preparation contains 4 mg. of Piptal and 6 mg. of phenobarbital in each ml. of a pleasantly flavored solution. The solution is administered directly into the mouth of the infant 15 minutes before feeding; the usual dose is 0.5 ml.; side effects are few. The pediatric Piptal preparation is contraindicated in cases of bowel obstruction.

Piptal is available in 5-mg. tablets. The usual dose is 5 to 10 mg., 4 times daily.

**Dibutoline Sulfate (Dibuline Sulfate).** This anticholinergic agent is a choline derivative and contains a quaternary nitrogen atom as shown in the formula:



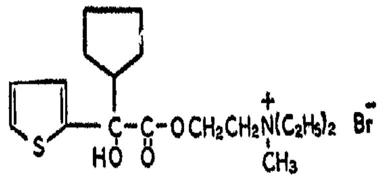
Dibuline Sulfate
(Di-*n*-butylcarbamic ester of dimethylethyl-β-hydroxyethylammonium sulfate)

Dibuline is a white, crystalline powder which is water soluble.

Dibuline is an anticholinergic agent which, like homatropine, has been used to produce *mydriasis* and *cycloplegia.* The ophthalmic solution is generally 5 per cent. Although weaker than homatropine for the purpose of refraction, the drug is said to produce fewer concomitant systemic effects.

Gruhzit and Moe (1949) studied the anticholinergic action of Dibuline. They observed that in addition to its anticholinergic activity Dibuline is capable of producing slight ganglionic blockade in larger doses. Cummins *et al.* (1947) showed that Dibuline was effective in inhibiting the spasm of the smooth musculature of the gastrointestinal tract. For this purpose the drug was administered intramuscularly in 5- and 10-mg. doses. Dibuline is not available for oral use.

**Penthienate Bromide (Monodral).** Monodral is a potent anticholinergic agent containing a quaternary nitrogen atom, as shown in the formula:



Monodral
(2-Diethylaminoethyl cyclopentyl-2-thienylhydroxyacetate methobromide)

Monodral is a white, crystalline powder which is freely soluble in water.

Monodral exhibits an anticholinergic activity against the acetylcholine-induced spasm of the isolated rabbit's ileum which is about ½ that of atropine (Ludueña and Lands, 1954). It decreases the tone and motility of the carbamylcholine-stimulated dog intestine to the extent of 53 per cent when administered in doses of 2 μg./kg. These spasmolytic doses in dogs elicited no central effects. Monodral produces only a slight mydriasis when instilled into the conjunctival sac of the cat.

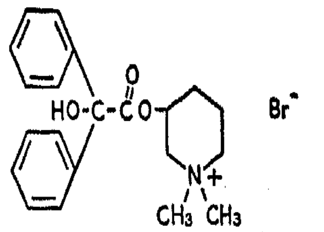
Monodral is effective in the treatment of peptic ulcer, hyperacidity, gastritis, and pylorospasm. Its spasmolytic action upon the colon is not marked. Kirsner and Palmer (1953) observed that 5 to 10 mg. of Monodral produced anacidity in 8 of 16 patients. Ingegno and Kertzner (1954) used Monodral in 29 ulcer patients. Good to excellent relief was achieved in 16, 7 of whom had not been relieved by other antispasmodics. Regression and healing of the ulcer niche was shown in 8 patients after 3 weeks of Monodral therapy.

Monodral appears to be well tolerated by most patients. Constipation, blurring of vision, and difficulty in voiding are uncommon. The dose is 5 mg., 3 to 4 times daily. Monodral is available in 5-mg. "caplets" and in an elixir containing 2.5 mg. in 5 ml. It is also provided in tablets containing 5 mg. of Monodral and 32 mg. of mephobarbital.

Steigmann and Dolehide (1955) studied comparatively propantheline, Antrenyl, Monodral, and Piptal on a series of 92 patients with various types of gastrointestinal disorders. They compared relief of clinical symptoms and diminution of gastric acidity. *Piptal,* 5 mg. every 6 hours, achieved symptom relief after 2 to 4 doses; *Monodral,* 5 mg. every 6 to 8 hours, elicited a similar response; *propantheline,* 15 mg. every 6 hours, was equally effective; *Antrenyl,* 5 mg. on a similar dosage schedule, appeared less prompt in alleviating symptoms. Mild xerostomia was experienced by a segment of the patients in each of the four groups.

The acidity curves dropped in 60 minutes after 10 mg. of Piptal; in 75 minutes after 10 mg. of Monodral or 30 mg. of propantheline. With 10 mg. of Antrenyl there appeared a greater depression of the acidity curve than was evoked by any of the other drugs.

**Mepenzolate Methylbromide (Cantil).** Cantil is another cholinergic blocking agent containing a quaternary nitrogen atom, as shown in the formula.



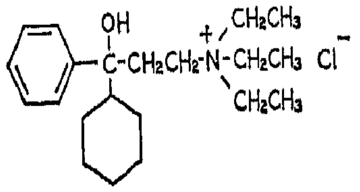
Cantil
(N-methyl-3-piperidyl diphenylglycolate methobromide)

Cantil is a while, crystalline powder which is sparingly soluble in water. Cantil was found to be the most effective anticholinergic agent among a large number of piperidols synthesized by Biel *et al.* (1953). The action of Cantil is mainly on the colon, on which it exerts a greater degree of antispasmodic activity than it does on the higher areas of the gastrointestinal tract. The pharmacology of Cantil was studied by Buckley *et al.* (1957); they found the anticholinergic activity of Cantil, 0.5 mg./kg., to be equal to or greater than 0.2 mg./kg. of atropine on the colon of dogs and cats. The duration of action of the two drugs was about the same. Cantil exhibited no significant antisialogogue activity and elicited no significant circulatory responses in normotensive dogs.

Clinical studies with Cantil have been reported by various investigators. Necheles *et al.* (1956) found Cantil effective in 17 of 18 patients treated for spastic colon. Riese (1957) found Cantil effective in 40 of 44 cases of irritable colon; using Cantil or the drug with phenobarbital, he observed remission of abdominal pain, distention, and diarrhea. Blurring of the vision and xerostomia were occasionally encountered, but were controlled by reduction of dosage. Urinary retention has been reported as a side effect with Cantil therapy.

Cantil is available in 25-mg. tablets and tablets of the same dose with 16 mg. of phenobarbital. The usual dose is 25 to 50 mg. 3 or 4 times daily while symptoms prevail, and 12.5 mg. 3 or 4 times daily as maintenance dosage.

**Tridihexethyl Chloride (Pathilon Chloride).** Pathilon chloride is a potent cholinergic blocking agent which contains a quaternary nitrogen in the molecule, as shown in the formula.



Pathilon Chloride
(3-diethylamino-1-phenyl-1-cyclohexyl-1-propanol ethyl chloride)

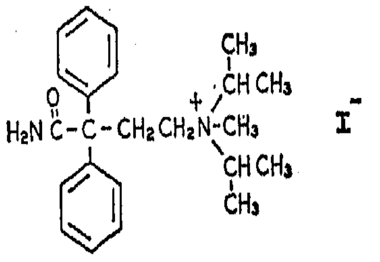
Pathilon chloride is a white, crystalline powder with a characteristic odor. It is readily soluble in water.

The pharmacologic responses to Pathilon resemble those elicited by other cholinergic blocking agents discussed in this chapter. Like other compounds in this series, its principal response is like that of atropine, and it is doubtful whether autonomic ganglionic blockade plays a role in its therapeutic effectiveness in the usual dosage regimen.

Pathilon is used therapeutically in the relief of pain resulting from spasm of the gastrointestinal tract. The side effects encountered in therapy with Pathilon are similar to those which occur with other drugs in this series. Generally the side effects can be minimized by the regulation of dosage. Blurring of vision, xerostomia, urinary retention, and tachycardia may be encountered with Pathilon therapy. Like most cholinergic blocking agents, Pathilon is interdicted in glaucoma.

The drug is not completely absorbed upon oral administration, and the parenteral dose is therefore much smaller than the oral dose. The oral dose is 25 to 50 mg. 3 or 4 times a day. The suggested parenteral dose is 10 to 20 mg. every 6 hours. Tablets containing 25 mg. are available, and an injection containing 10 mg. in 1 ml. of Pathibamate contains 25 mg. of Pathilon with either 200 or 400 mg. of meprobamate.

**Isopropamide Iodide (Darbid).** Darbid is a newer cholinergic blocking agent which appears to offer the advantage of low dosage and long duration of action. It contains a quaternary nitrogen atom in the molecule, as shown in the formula:



Darbid
[(3-Carbamoyl-3,3-diphenylpropyl) diisopropylmethylammonium iodide]

Darbid is a white, crystalline powder which is readily soluble in water.

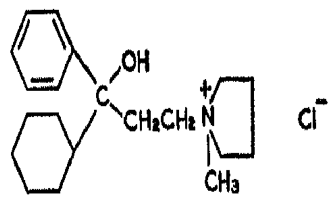
The pharmacologic responses to Darbid are mainly atropine-like in character. In therapeutic doses autonomic ganglionic blockage is not a component of its action. Darbid evokes potent antispasmodic and antisecretory activity which is estimated to last for 12 hours.

Darbid is used therapeutically in the relief of pain resulting from spasm of the gastrointestinal tract. It appears to have special value in preventing the nocturnal secretion of gastric acid in patients with peptic ulcer. Blurring of vision, xerostomia, and urinary retention are encountered as side effects. Like other cholinergic blocking agents, Darbid is contraindicated in glaucoma.

Shutkin (1958) obtained good to excellent results with Darbid in 26 of 30 cases of peptic ulcer. Side effects of a mild character were encountered in 6 patients. The dosage schedule was 10 mg. every 12 hours. Experimental studies on 10 patients with chronic duodenal ulcers indicated that Darbid was more effective than propantheline in suppressing the volume and acidity of gastric secretion under basal conditions and upon histamine stimulation.

Darbid is available in 5-mg. tablets. The usual adult dose is 5 mg. every 12 hours.

**Tricyclamol Chloride (Elorine Chloride).** Elorine is a potent anticholinergic agent also eliciting autonomic ganglionic blocking action. Its structure is shown in the following formula:



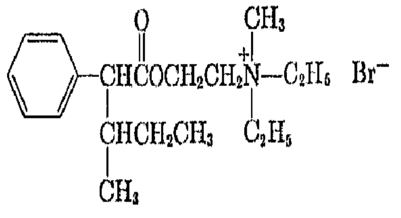
Elorine Chloride
Tricyclamol Chloride
(1-phenyl-1-cyclohexyl-3-pyrrolidino-1-propanol methyl chloride)

The principal action of Elorine is that of producing vagal block of the smooth muscle of the gastrointestinal tract. Like other anticholinergic agents, Elorine reduces the flow of gastric juice, saliva, and pancreatic secretions. Elorine also inhibits the cardiac vagus. High doses of Elorine evoke a curare-like action of skeletal muscle. The acute toxicity of Elorine is low ($LD_{50}$ is about 984 mg./kg. in the rat), and the central nervous system-excitatory effect of large doses of atropine is not produced by Elorine.

Lin *et al.* (1959) found that 1 mg./kg. of Elorine, when administered orally, inhibited the basal secretion of gastric juice in rats. The meal-and-insulin-stimulated gastric secretion of the innervated and denervated gastric pouches of dogs were depressed by 1 to 2 mg./kg. of Elorine. The inhibition was in total volume and in acid concentration. Elorine was less effective in inhibiting histamine-induced gastric secretion. These investigators conclude that the inhibitory effect of Elorine on gastric secretion is mainly on the neurohumoral mechanism rather than the humoral mechanism (histamine or gastrin) of the gastric acid secretion.

Elorine is recommended in conditions of hypermotility of the gastrointestinal tract, peptic ulcer, and colitis. Various clinical reports indicate that Elorine is effective in peptic ulcer and in the irritable colon syndrome. Symptomatic relief is usually achieved with doses of 25 to 50 mg. 3 times daily. Side effects with Elorine are similar to those elicited by other anticholinergic agents of this class. They include xerostomia, blurring of vision, and a tendency toward urinary retention.

**Valethamate Bromide (Murel).** Murel is a potent anticholinergic agent containing a quaternary nitrogen atom. It is also claimed to evoke a direct relaxant action on smooth muscle. Chemically the compound is 2-diethylaminoethyl 3-methyl-2-phenyl-valerate methylbromide, as shown in the formula:

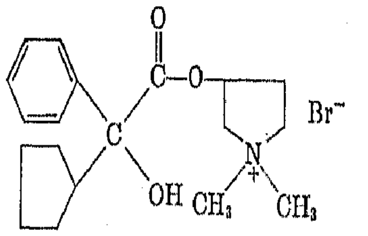


Valethamate Bromide
Murel

Murel is indicated in spasm of the gastrointestinal, genitourinary, and biliary tracts. It is also useful in the treatment of peptic ulcer. From the data available Murel appears to be a reliable and competitive anticholinergic drug. Evidence of superiority has not been established. The side effects encountered are identical with those of the other anticholinergic drugs.

Murel is administered intravenously or intramuscularly in doses of 10 to 20 mg. for acute smooth muscle spasm. For treatment of ulcer, 10-mg. tablets are available, and 1 to 2 tablets 4 times daily is the recommended dose.

**Glycopyrrolate (Robanul).** Robanul is a newer and powerful anticholinergic agent of type structure containing a quaternary nitrogen atom, as shown in the formula:



Glycopyrrolate
Robanul
(1-methyl-3-pyrrolidyl $\alpha$-cyclopentane-glycolate methobromide)

Moeller (1962) describes the molecular structure of the compound as follows: "It consists of a rigid ring molecule in which the nitrogen in the cationic head is held at a fixed distance from the high electron density carbonyl group." It is postulated that this rigidity of molecular structure enhances the molecule's "fit" at cholinergic receptor sites.

Robanul is recommended for its potent antispasmodic activity on the gastrointestinal tract. Slanger (1962) found the drug effective in 46 of 50 patients with various gastrointestinal disorders involving spasm and hypersecretion. He observed antisecretory as well as antispasmodic activity. Two patients experienced drug-related dermatologic reactions. Of special interest was the absence of xerostomia, blurred vision, or urinary retention. It will be interesting to observe whether this somewhat new molecular approach will achieve therapeutic superiority.

Robanul is available in 1-mg. tablets. The daily dose is 3 to 8 tablets.

### Choice of an Anticholinergic Agent

Atropine and its closely related compounds, such as hyoscyamine and homatropine methyl bromide, remain the drugs of choice among many gastroenterologists in the treatment of hypermotility of the gastrointestinal tract. The older atropine substitutes without quaternary nitrogen atoms, such as Trasentine and Syntropan, are also used. They serve well in many cases where the side effects of atropine complicate therapy. Nevertheless, it must be recognized that the new anticholinergic agents have markedly contributed to the success in ulcer therapy. They have increased the anticholinergic activity comparable to that of atropine on a weight-to-weight basis, and because of less toxicity larger dosage schedules and hence more effective cholinergic blockade are permissible.

A drug of choice among them can certainly not be determined today from clinical data available. It does appear that it is a matter of "tailor-fitting" the drug to the patient's needs, and further, of employing the drug with which therapy in the individual patient is fraught with the fewest side effects.

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# 38

# *Autonomic Ganglionic Depressants. Nicotine and Quaternary Ammonium Compounds*

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In the preceding chapters our attention has been called to the action of acetylcholine on all autonomic ganglia. It stimulates these structures in small doses and depresses in larger doses. This has been referred to as the ganglionic or "nicotinic" action of acetylcholine. Acetylcholine mimics the action of nicotine on autonomic ganglia and also on skeletal muscle. Our interest lies in nicotine not only because it is a ganglionic stimulant and paralysant (and as such a valuable pharmacologic tool) but also on account of the widespread use of tobacco which contains this alkaloid.

In addition to nicotine, certain quaternary ammonium compounds such as tetraethyl ammonium chloride exhibit a marked specific action on autonomic ganglia. These compounds depress autonomic ganglia and have been introduced into clinical medicine by virtue of this effect.

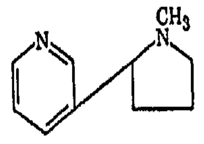
We shall consider first the alkaloid nicotine.

## NICOTINE

Nicotine is an alkaloid obtained from *Nicotiana tabacum*, a leafy plant belonging to the potato family. The plant was known to the American Indians and was smoked by them at the time of the discovery of America. The nicotine content of the dried tobacco leaves varies between 1 and 8 per cent. The alkaloid was first observed in tobacco smoke by Vauquelin (1809), and its nature was established by Posselt and Reimann (1829). In the leaf the alkaloid is combined with malic and citric acids. The alkaloid was named "nicotine" in honor of Jean Nicot, an ambassador of the King of France in the mid-sixteenth century. He received the tobacco plant from Florida, planted it in Portugal, where it grew abundantly, and used the leaves in the treatment of a variety of skin lesions.

The pure, uncombined alkaloid is a colorless, oily liquid. It becomes gradually brownish as it is exposed to the air. Nicotine elicits an acrid, pungent odor suggestive of amine bases. It is alkaline in reaction and irritating to the skin. The alkaloid is miscible with water and very soluble in alcohol and the ethereal solvents.

The structure of nicotine is shown in the formula below.



Nicotine
(pyridyl-N-methylpyrrolidine)

Certain salts of nicotine, such as the hydrochloride, are white, crystalline solids which are readily soluble in water.

**Response of the central nervous system.** In any discussion of the pharmacologic responses to nicotine, it is imperative to point out in the very beginning that nicotine is a *violent poison.* The entire central nervous system, after an incipient period of stimulation, is markedly depressed by nicotine. The paralysis is descending in character and may resemble the effects of hypoxia.

The effects on the cerebral hemispheres are not marked, but the medullary action is striking. The effect on respiration is prompt. Small doses will produce a transient stimulation reflexly through the carotid body, but larger doses rapidly bring the respiration to a standstill. This is generally the cause of death in nicotine poisoning. The respiratory arrest produced by nicotine is due to the paralysis of the diaphragm and chest muscles through the blockade at the neuromuscular junction. Gold and Modell (1936) showed that in respiratory arrest caused by nicotine the respiratory centers were still capable of discharging impulses through the phrenic nerves.

The spinal centers are generally stimulated sufficiently to produce convulsions. These contribute also to the fatal asphyxia. The action of nicotine on the spinal cord may be observed by applying directly an 0.1 per cent solution of the alkaloid to the spinal cord of a frog. Generalized twitchings in skeletal muscle are observed. The vagal, vasoconstrictor, and vomiting centers are first strongly stimulated and then paralyzed.

**Effects on the autonomic ganglia.** The ganglia of each division of the autonomic nervous system are stimulated by small doses of nicotine. Larger doses produce paralysis following the initial stimulation. This paralysis has been mentioned frequently as a means of determining the locus of action of other drugs. For example, the inhalation of ammonia produces reflex stimulation of the vagal center and cardiac slowing. This cardiac slowing is blocked by nicotine. Picrotoxin directly stimulates the vagal center, slowing the heart. Its action is blocked by nicotine. Thus one observes that stimuli that must pass from the preganglionic to the postganglionic fibers are blocked by nicotine. Nicotine blocks the ganglionic-stimulating action of small doses of acetylcholine but not its peripheral vasodilating effect. Nicotine does not block the action of pilocarpine in stimulating the effector cells of the vagus nerve in the heart. This action is peripheral to the ganglionic action of nicotine and is not dependent upon the impulses being transmitted over the autonomic synapse.

The nature of the autonomic ganglionic action of nicotine has been studied critically by numerous investigators. Paton and Perry (1953) studied the relationship between depolarization and blocking of the cat's superior cervical ganglion evoked by nicotine. Nicotine constantly produced a transient depolarization, but the block was usually prolonged. During the blocking phase the ganglion was refractory to doses of nicotine that ordinarily elicited depolarization. They suggest that the blocking action is of a competitive type. Trendelenburg (1957) holds the view that the blocking action of nicotine is not of the competitive type, since ganglionic stimulants which are not nicotine-like (potassium chloride, histamine, and pilocarpine) are capable of ganglionic stimulation during the blocking phase of the action of nicotine. Supporting this latter concept is the work of Pelikan and Carter (1962), who contend that the prolonged impairment of ganglionic blockade with nicotine is caused by a decrease in the release of acetylcholine from the presynaptic nerve terminals, rather than by occupation of the postsynaptic ganglionic receptors.

The autonomic ganglionic action of nicotine is specific; its action on synaptic conduction in the spinal cord is less specific, and its action appears to be controversial. Nicotine depresses the patellar reflex in animals, while the flexor reflex is relatively unaffected. It appears that monosynaptic activity is depressed by nicotine, while multisynaptic activity is not appreciably depressed and might even be facilitated.

**Circulatory effects.** Nicotine produces a marked effect upon the circulatory system. The intravenous injection of diluted nicotine solutions into the usual laboratory animals affects the pulse rate in the following manner. Through the incipient stimulation of the vagal ganglionic cells the heart is first slowed, later accelerated through the paralysis of these same cells. Simultaneously, the ganglionic cells of the sympathetic accelerator nerve are stimulated and depressed. The vagal effect, however, predominates. In the atropinized animal the vagal effects are obliterated and cardiac acceleration is the initial response. Preliminary slowing of the heart does not usually occur. The cardiac slowing caused by nicotine through vagal stimulation is not entirely ganglionic. A component in the response is the stimulating effect of nicotine on the vagal center through the carotico-aortic mechanism. After repetitive doses of nicotine the paralyzing effect on the vagal ganglionic cells remains manifest, and the heart rate is consequently accelerated.

Small doses of nicotine raise the blood pressure. The response is mediated through the stimulation of the sympathetic ganglionic cells, the postganglionic fibers of which are constrictor to the arteries. But in addition to other factors in the response are the stimulation of the vasoconstrictor center and release of epinephrine. The rise in blood pressure is evanescent. The continued administration of nicotine finally evokes a depressor response. The sympathtic ganglionic cells are then paralyzed, and stimulation of the splanchnic nerves produces no pressor response. The blood pressure falls further with repeated doses and the pulse rate is accelerated.

Westfall and Watts (1963) showed that the inhalation of cigarette smoke by dogs caused a significant increase in epinephrine levels of the adrenal vein, vena cava, and peripheral arterial and venous blood. The degree of increase was greatest in the adrenal vein, and blood samples from other areas showed progressively less epinephrine increase.

**Effect on the gastrointestinal tract.** The incipient effect of small doses of nicotine on the musculature and secretory glands of the gastrointestinal tract is one of stimulation. Salivation, gastric secretion, and frequently nausea and vomiting are produced. Through preliminary stimulating effects on the intestinal vagal ganglia, peristalsis is produced.

These effects are very often observable in the uninitiated smoker. Marked salivation occurs. This has been repeatedly studied in laboratory animals in the following manner. A cannula is inserted in the submaxillary duct. The chorda tympani is stimulated, and a copious flow of limpid saliva results. Nicotine in small doses is given. Its effect mimics the stimulation of the chorda tympani and serves as a sialogogue. If larger doses of nicotine are injected, electrical stimulation of the preganglionic fibers of the chorda tympani elicit no response. However, the injection of pilocarpine which acts peripheral to the ganglion elicits salivary flow by stimulating the effector cells in the gland. This flow is checked by atropine, whose site of action is the same as that of pilocarpine.

**Effect on skeletal muscle.** Fibrillary twitching in skeletal muscle is produced by nicotine injections. These occur after the nerve supply to the muscle has been severed. The contracting action is likely to occur at the neuromuscular junction. It is effectively blocked by curare. Like the action of nicotine on other structures, larger doses produce paralysis of the skeletal muscle (Fischer *et al.*, 1960).

**Effect on urine flow.** Nicotine and its metabolites are excreted in the urine by the kidneys. Mention of the deleterious effects of nicotine on the functional activity of the kidneys is conspicuous by its absence in the vast literature on the effects of this alkaloid. However, evidence emanating from various sources indicates that nicotine exerts an antidiuretic effect. This action is mediated through stimulation of the posterior lobe of the pituitary to release the antidiuretic hormone (ADH). The quantities of nicotine absorbed in tobacco smoke are capable of eliciting this effect in "well-hydrated" individuals. Since the hypothalamic mechanisms are sensitive to small doses of nicotine, as demonstrated by the antidiuretic effect, it is possible that the regions of the hypothalamus concerned with hunger and satiety (see page 477) are also influenced by its action. This in turn might be a facet of the action involved in the appetite changes which accompany smoking and abstinence (Silvette *et al.*, 1960).

**Fate in the body.** Nicotine injected into laboratory animals or inhaled by man from tobacco smoke is partially degraded in the body. The remainder is excreted in the urine unchanged. A major site of detoxification of nicotine in the

body is probably the liver. Haag and Larson (1944) showed that animals whose livers had been injured by carbon tetrachloride exhibited less resistance to the toxicity of nicotine than did normal animals. Miller and Larson (1953) in studies on tissue slices found liver tissue most active in the degradation of nicotine, while kidney and lung were less active, and brain tissue was inactive. Hucker *et al.* (1959) showed that the major site of the degradation of nicotine was in the liver and that this was achieved by the microsomes by an enzyme system requiring reduced triphosphopyridine nucleotide and oxygen. They suggested that the first step in the oxidation of nicotine is hydroxylation, which is followed by oxidation to *cotinine* and subsequent hydrolysis. Similar observations were made by Bowman *et al.* (1959), who identified cotinine in the urine of subjects who smoked tobacco or ingested nicotine. The suggested presence of hydroxycotinine and desmethylcotinine in the urine indicates that cotinine plays an important role in the metabolism of nicotine in man.

Haag and Larson (1942) found that the quantity of nicotine excreted in the urine of smokers varied with the pH of the urine. At an average urinary pH of 7.1 to 7.6, 2.3 to 3.7 per cent of nicotine, calculated to be retained from tobacco smoke, was excreted in the urine. At pH 4.9 to 5.7, 9.8 to 13.0 per cent of the nicotine was excreted. These investigators hold the view that the difference is due to decreased reabsorption of nicotine from the urinary tract with increasing urinary acidity.

Larson and Haag (1942) found that the injection of 3 mg./kg. of nicotine subcutaneously into dogs led to a total urinary excretion of about 10 per cent of the total nicotine administered.

Finnegan *et al.* (1947b) showed that when the dosage of nicotine in dogs was increased, the total percentage of nicotine excreted in the urine was also augmented. They found that the relationship between increased dosage and increased urinary excretion was linear. On the other hand, the relationship between nicotine dosage and nicotine detoxification was logarithmic. It is of interest that the urinary excretion of nicotine is usually complete 16 hours after discontinuing the administration. Larson *et al.* (1949) studied the excretion rates of nicotine in the dog, mouse, cat, and rabbit. They observed much variation in the excretion rates of nicotine by these different species of animals. The cat was capable of excreting nicotine more rapidly than the other species studied.

The data of Perlman *et al.* (1942), obtained among smokers, essentially agree with the experimental findings of Haag and his associates. In smokers it was observed that there existed a definite correlation between the number of cigarettes smoked and the concentration of nicotine in the urine.

**Tolerance to nicotine.** Animals and people rapidly develop a tolerance to nicotine. The excitation, salivation, and nausea disappear, and the burning sensation of the buccal membranes diminishes upon the repetitious use of tobacco containing nicotine. Wahl (1920) found that uninitiated individuals are nauseated by 1 to 2 mg. of nicotine administered orally. Habitual smokers, however, could tolerate about 8 mg. of the alkaloid.

**Acute nicotine poisoning.** There is no therapeutic application of the action of nicotine. Acute poisoning, therefore, does not occur from overdosage in the medicinal use of the alkaloid. The crude sulfate of the alkaloid is sold as an insecticide in a solution known as "Black Leaf 40." For this purpose it is effective and kills insects by direct paralysis, ascending the ventral nerve cord from the abdomen to the brain. Because of this use of the alkaloid, cases of nicotine poisoning occasionally occur from accidental or intentional ingestion of the insecticide solution.

Other possible sources of nicotine poisoning are the prolonged inhalation of tobacco dust and contact with the alkaloid during the tobacco extraction process.

The toxic syndrome following oral ingestion is marked by a severe burning sensation of the buccal membranes, throat, and stomach. Salivation, vomiting, and diarrhea are likely to occur. The individual is at first markedly excited, with a rapid respiration. This is followed by depression, rapid pulse, incoordination, and shallow and slowed respiration. Consciousness is lost, and death occurs from respiratory arrest through paralysis of the respiratory muscles.

The treatment of acute nicotine poisoning should be instituted as follows: The stomach should be lavaged to remove any alkaloid that has not been absorbed. Artificial respiration is the principal restorative measure, and this should be accompanied by measures supportive to the circulation. If cardiac stoppage occurs, epinephrine should be employed by intracardiac injection (see page 548).

### The Tobacco Smoking Habit

As it was stated previously, the smoking of tobacco was a habit among the American Indians when the North American continent was settled by Europeans. Smoking was introduced in England in the early part of the seventeenth century. Sir Walter Raleigh was a tobacco enthusiast. The use of tobacco spread rapidly throughout Europe. At first smoking of tobacco was believed to confer medicinal benefit upon the individual, but later it was considered as a luxury. In medical practice of the past centuries tobacco was considered a drug with medicinal virtues, valuable in the treatment of many diseases. It was designated as the *herba panacea*. Indeed, as late as 1890 tobacco was official in the U. S. Pharmacopeia. The spread of the tobacco smoking habit was not confined to Europe. The plant was imported and also cultivated in other countries, and smoking tobacco is prevalent today among the oriental peoples.

The United States grows more tobacco than any other country. This country produces from ⅓ to ½ of the world's supply of the tobacco leaf. In 1962 about 6.5 billion cigars and over 543 billion cigarettes were manufactured in the United States. This figure is the equivalent of 7 to 8 cigarettes a day per person. The tobacco industry grossed 7.5 billion dollars. The Federal tax on tobacco which was collected in 1962 was 2.03 billion dollars.

It is of interest that man clings tenaciously to the drinks which affect his central nervous system, *viz.*, alcohol, coffee, and tea. The substances which he smokes, such as opium, marihuana, and tobacco, also affect him psychically. The German word "Genussgift" has been applied to nicotine as a constituent of tobacco. It means "poison of enjoyment." It tranquilizes the troubled spirit. Finnegan *et al.* (1945) fittingly commented regarding the use of tobacco: "One becomes used to combating with nicotine, hunger and thirst, joy and pain, heat and cold, irritation and languidness."

The literature of the advocates and of those who condemn the use of tobacco is voluminous. In this discussion we shall attempt to confine our comments to the following problems of special clinical interest:

1. In which diseases is smoking interdicted?
2. What is the consensus regarding the nervous reactions, general health, and longevity of smokers?
3. What are the toxic products of tobacco smoke?
4. What is the difference between the various forms of tobacco smoking and inhalation?

**Diseases in which smoking is contraindicated.** In the foregoing paragraphs it has been stated that nicotine produces peripheral vasoconstriction. Further, this effect results in an increased arterial tension. In addition, cardiac acceleration may occur concomitantly.

Weatherby (1942), in a carefully controlled series of cases, showed that the smoking of 1 cigarette by a habitual smoker produced the following changes:

1. Increase in systolic blood pressure of 10 to 25 mm.
2. Acceleration of pulse of 5 to 20 beats per min.
3. Drop in skin temperature of 2 to 5°C (finger), 3 to 7°C (toe)

The effects are transient and as a rule last for only a few minutes. The complete removal of nicotine from the cigarette abolishes most of the foregoing effects. The restoration of nicotine reestablishes the circulatory changes. These effects were obtained on individuals who were lightly covered and in a resting state. Many of the foregoing effects of nicotine are not apparent when the subject is engaged in mild physical activity.

The foregoing circulatory effects of nicotine absorption by smoking have been observed by various investigators. It would follow, therefore, that in the following disease conditions smoking is contraindicated:

1. In *Buerger's disease* (thrombo-angiitis obliterans), where painful peripheral vascular inflammation and vasoconstriction are present in the extremities, tobacco producing further peripheral vasoconstriction will aggravate the condition.

2. In *Raynaud's disease* (symmetrical gangrene), where peripheral circulation is impaired, tobacco is interdicted.

3. In *hypertension*, especially when this is associated with *tachycardia*, the nicotine in tobacco cannot be considered a benign product of absorption.

4. In *postcoronary conditions* and *angina pectoris* tobacco is often forbidden. Many studies have shown that nicotine dilates the coronary arteries, probably through the release of catecholamines from chromaffin tissue stores. However, in coronary insufficiency disease, the degree of dilatation does not compensate for the increased work load imposed upon the heart through cardiac acceleration and increased blood pressure. Although it has been suggested that smoking increases the level of blood lipoproteins and cholesterol, this has not been definitely established.

5. In *peptic ulcer* the use of tobacco is generally forbidden. Nicotine in some individuals has an excitatory effect upon gastric secretion and therefore is prone to increase gastric acid. Assuming that the vasoconstriction in the periphery is shared by the vessels supplying blood to the gastrointestinal tract, nicotine would be objectionable. One of the hypotheses regarding the occurrence of ulcer holds that autonomic imbalance giving rise to localized areas of ischemia in the gastrointestinal tract is responsible for the erosion and ulceration.

6. *Bronchial coughs* are often aggravated by smoking, and in this condition tobacco is interdicted. It is well known that the excessive use of tobacco, especially inhalation of smoke, may produce a so-called "smoker's cough," and if irritation of the membranes is present it is made more severe by the irritating properties of tobacco smoke.

7. Frazier *et al.* (1961) studied the relationship between smoking and *premature births*. Their study involved 2736 Negro women who were delivered of live-born single infants. The prematurity rate was 18.4 per cent for those who smoked, compared with 11.2 per cent for nonsmokers (including occasional smokers). The rate of prematurity increased with the amount of smoking.

**Smoking, general health, and longevity.** There have been many studies conducted to show the effect of smoking tobacco on mental alacrity. Although in general the effects are not striking, the preponderance of evidence seems to indicate that if an effect exists, it is deleterious rather than helpful. There are so many other factors involved that influence mental acuity and efficiency that we are inclined to believe that moderate smoking has no demonstrable effect upon psychic acuity or over-all mental achievement.

As a rule, smokers have less favorable nervous reactions than nonsmokers. Habitual heavy smoking occasionally produces a hand tremor, and the tremor becomes more noticeable after intense smoking. It has been reported that smoking intensely has diminished the accuracy of target shooting and similar performance tests.

Nonsmokers are often capable of remaining quiet and keeping their attentions focused for longer periods than are smokers. The smoker becomes fidgety and restive. He must get up and walk around or have a smoke. The smoke confers a tranquilizing effect, enabling him to remain in a state of repose and attentiveness. It is difficult to incriminate tobacco entirely in this type of unfavorable nervous reaction. It was probably restiveness and anxiety that prompted smoking initially. One cannot gainsay that in states of emotional distress such as those caused by bodily injury or intense concentration at examination time, smoking does not confer a desirable tranquility of spirit.

Whether or not the smoking of tobacco will cause the vascular disturbances in which it is forbidden is polemic. That coronary disease occurs most frequently in heavy smokers is not *prima facie* evidence that it is responsible for the disease. Since the psychic state and personality of the individual are important factors in tobacco smoking, the role of smoking as such as a cause of coronary artery atherosclerosis remains undetermined. It is not clear whether excessive smoking augments the coronary disease process or merely reflects some basic psychologic stress.

The effect of smoking on longevity is always a captivating subject. Data which are convincing are difficult to obtain. Pearl (1938) studied this problem, including observations on 6813 men. He classified the individuals into three groups as follows:

1. Nonsmokers
2. Moderate smokers
3. Heavy smokers

No person in the group used tobacco by chewing. His findings were as follows: ½ of the heavy smokers were dead in 17½ years after the starting age of 30 years. It was 26 years before ½ of the moderate smokers were dead, and 28 years before ½ of the nonsmokers died. This strongly suggests the inadvisability of heavy smoking. When the survivors reached 70 years of age, the statistical advantage of the nonsmokers disappeared. Pearl states: "Those who survive to

70 or thereabouts are such tough and resistant specimens that thereafter tobacco does them no further measurable harm as a group." Pearl's findings emphasize that people differ in susceptibility to tobacco by inheritance. These inherited traits, either as specific metabolic patterns or as more or less sensitive autonomic nervous systems, manifest themselves in the resistance of different individuals to nicotine. It is therefore extraordinarily dangerous to make glowing generalities. Each person is different, and it is surprising not that various people respond differently to the poisonous alkaloid nicotine, but that so many differently constructed individuals react alike.

For the purpose of emphasis at this point we repeat the statement of the savant Heraclitus (see page 43): "No man can step in the same river twice."

**Toxic products of tobacco smoke.** Tobacco smoke is a dense aerosol consisting of millions of semi-solid particles per ml. of the gaseous phase. When a typical 70-mm. domestic all-tobacco cigarette is smoked according to a standard procedure, the cigarette yields about 33 mg. of particulate phase smoke and about 15 times this amount of gaseous phase smoke. When tobacco is burned the smoke contains nicotine, pyridine bases, hydrocyanic acid, ammonia, carbon dioxide, carbon monoxide, organic acids, aldehydes, hydrocarbons, so-called "tobacco tar and resin," and other constituents of minor importance. The quantities of hydrocyanic acid present are insignificant and therefore do not alter the irritating properties or toxicologic effects of the smoke. The smoke that enters the smoker's mouth is distinctly acid, owing to the presence of organic acids. In contrast, the smoke which escapes into the atmosphere from the burning tip is alkaline, owing to greater completeness of combustion and the presence of larger quantities of ammonia. The quantities of carbon monoxide present in tobacco smoke are of minor importance.

It appears, therefore, that the agent present in tobacco smoke responsible for most of the pharmacologic symptoms is principally nicotine. Haag (1940) found that the intravenous injection of cigarette smoke solutions produced the same blood pressure responses in the anesthetized dog as did the injections of nicotine acetate solutions of the same nicotine content. The toxicity of the smoke solutions was slightly greater to mice upon intraperitoneal injections than solutions of nicotine acetate of the same nicotine content. Haag believed that the difference was due to other irritants in the smoke which produced vasodilatation and promoted absorption. It is of special interest that the pressor response in the dog to tobacco smoke was found to be proportional to the nicotine content of the tobacco undergoing ignition. Haag states: "The actions of cigarette smoke solutions, as regards their acute toxicities and their effects on blood pressure by intravenous injection, are due to their nicotine content."

Tobacco is treated with hygroscopic agents such as glycerin or certain glycols for the purpose of enabling it to retain its moisture more tenaciously. Much discussion in recent years has been carried on regarding the irritating properties of these agents in tobacco smoke. Finnegan *et al.* (1947a) developed an ingenious method to determine quantitatively the irritative properties of tobacco smoke. They exposed the eyes of morphinized albino rabbits to the smoke for definite time periods. The membranous lining of the upper lid responded to the irritation by becoming edematous. The membrane was then excised and the degree of edema determined by the water content of the membrane, which was ascertained gravimetrically. They found that the hygroscopic agents glycerin and diethylene glycol did not significantly alter the irritating properties of the smoke. The loose packing of tobacco, as well as the removal of moisture from the tobacco, significantly increased the irritating properties of tobacco smoke. Cigarettes of the same brand are sufficiently uniform in composition to produce smoke of rather constant irritating properties. The smoke from different brands of cigarettes may show measurable variation in their capacity to produce mucous membrane irritation.

The evidence is clear that tobacco smoke is irritating to mucous membranes. The question whether this repetitious irritating action produces neoplastic growth is an important one. Its answer is not readily available. An increased incidence of cancer of the lip and tongue has been reported among heavy smokers. Nevertheless, the great increase in the use of tobacco in recent years by women and men has not been matched by a concomitant increase in cancer of the oral cavity. Of interest is the fact that Roffo (1941) obtained a carcinogenic substance from tobacco tar that produced stomach cancer in $\frac{1}{2}$ of the rats to which it was administered by mouth daily.

Shrek *et al.* (1950) studied the smoking habits of 82 men with cancer of the lung and 73 men with cancer of the larynx and pharynx. These were compared with a control group of 522 patients with miscellaneous tumors. A relatively high percentage of cigarette smokers was found among the patients with cancer of the respiratory tract, as compared with the control group. The positive correlation between the incidence of cancer of the respiratory tract and cigarette smoking appeared to be statistically and biologically significant. These investigators state: "There is strong circumstantial evidence that cigarette smoking was an etiologic factor in cancer of the respiratory tract."

**Smoking and bronchogenic cancer.** Sadowsky *et al.* (1953) studied the retrospective smoking histories of 1990 patients with cancer of the lip, tongue, pharynx, esophagus, larynx, and lung. These were compared with those of 615 patients with illnesses other than cancer. Their data were analyzed statistically. From these they concluded that there was statistical association (1) between pipe smoking and cancer of the lip, (2) between cigarette smoking and laryngeal cancer, and (3) between cigarette smoking and cancer of the lungs. These investigators were primarily concerned with smoking and cancer of the lungs. In this study the rate of incidence of lung cancer was 5 times greater among smokers than among nonsmokers.

Evidence appears to be accumulating that cigarette smoke contains the carcinogen 3,4-benzpyrene. It is estimated by various workers that the smoke from 100 cigarettes contains 1 $\mu$g. of this hydrocarbon. Cooper and Lindsey (1955) estimate that 0.05 $\mu$g. of 3,4-benzpyrene is contributed by the combustion of the paper and the remainder from the burning tobacco. Anthracene and pyrene, noncarcinogenic hydrocarbons, are present to the extent of approximately 10 $\mu$g. each in the smoke of 100 cigarettes.

Since 3,4-benzpyrene is also present in the air in highly industrialized communities, the question arises whether or not this too is not a factor in the pathogenesis of bronchogenic carcinoma.

Stocks and Campbell (1955), in their studies of causative factors in the etiology of lung cancer in the British Isles, related the death rates to the presence of benzpyrene and other noxious substances in the air. This they found was an additive factor to cigarette smoking. Rural death rates from lung cancer were lower than those in Liverpool. The Liverpool rates exceeded the rural rates in people in each smoking category. The striking figure was the urban/rural ratio of 9 to 1 among nonsmokers. Their studies strongly suggest the air contaminants as an additive factor to cigarette smoking in the cause of lung cancer. Kotin and Falk (1959) identified 3,4-benzpyrene, one of the carcinogens in tobacco smoke, as a contaminant in the polluted air of Los Angeles. They stated: "From an experimental point of view, polluted air meets the criterion for being strongly suspected as one of the factors responsible for the increasing incidence of lung cancer." Thus it appears that along with the incrimination of tobacco smoke as an etiologic factor in lung cancer, air pollution must also be considered.

Hammond and Horn (1954) observed a direct relationship between death rates and smoking habits. The death rate was found to be 52 per cent higher among men with heavy cigarette smoking habits than among nonsmokers. Lung cancer and coronary artery disease were foremost among the causes of death. While these data are suggestive, they do not provide conclusive evidence of a causative relationship. The data of these investigators (1958) in a 24-month follow-up study confirmed their previous findings. The death rate of men with a history of regular cigarette smoking was 68 per cent higher than that of a comparable group who never smoked. The death rate appeared to be a function of the number of cigarettes smoked.

Wynder (1955) states: "Tobacco smoking, and especially cigarette smoking, plays a role in the causation of lung cancer. This statement does not deny the role of other factors in the development of this disease."

The 1955 survey of the medical and scientific division of the American Cancer Society with regard to the correlation between cigarette smoking and lung cancer voiced the following opinions: 55 per cent of those questioned agreed with the statement that "heavy cigarette smoking may lead to lung cancer." Only 5 per cent took exception to this statement, 32 per cent expressed uncertainty, and 8 per cent did not reply.

Germane to this subject is the report of the United States Department of Health, Education, and Welfare by Dorn (1959). This study embraces data on 200,000 policy holders of United States Government life insurance with regard to tobacco consumption and mortality from cancer and other

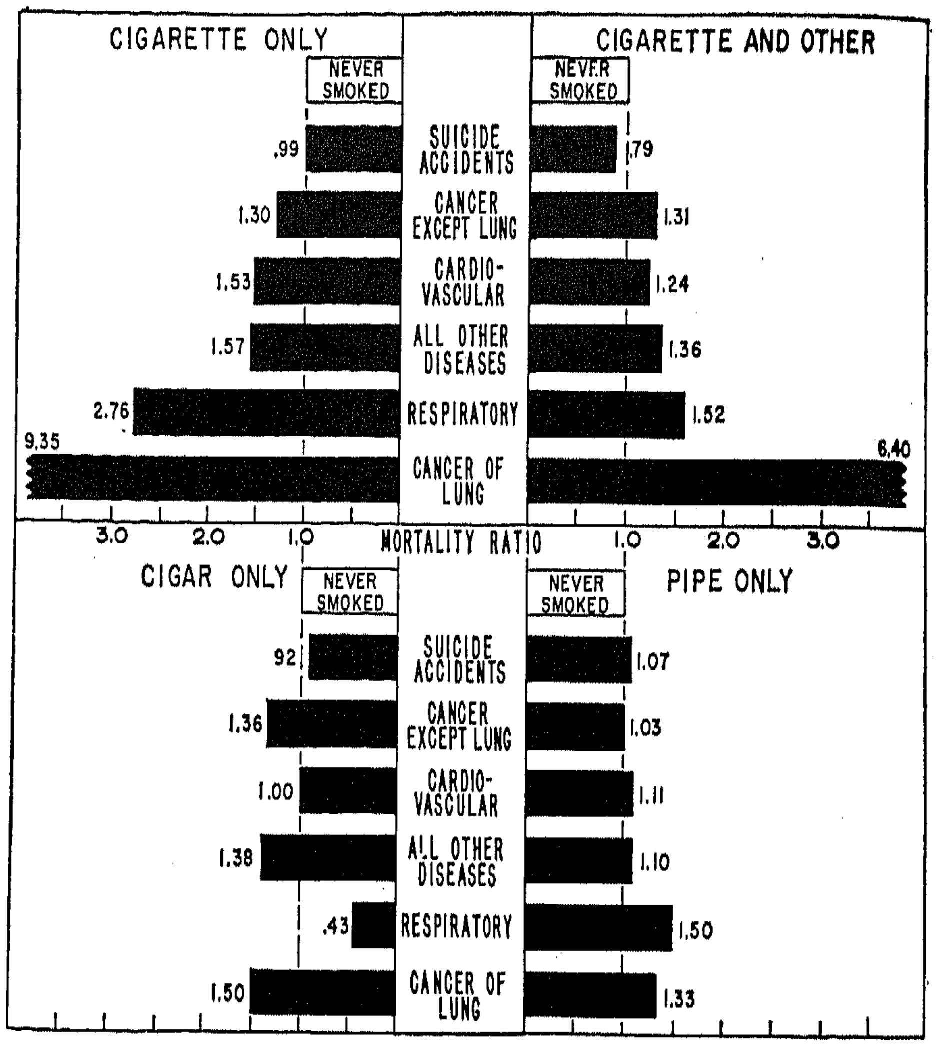


FIG. 38-1. Mortality of smokers from broad groups of causes of death; ratio of observed to expected number of deaths; death rate of nonsmokers and persons who have smoked only occasionally equals 1.00. (From H. F. Dorn, Pub. Health Rep., **74:** 581, 1959.)

diseases. The essential findings of this study are shown in figure 38-1.

Implicit in these data is the fact that the greatest increase in the risk of developing a disease for smokers is cancer of the lung. The risk for regular smokers of cigarettes is about 10 times that for nonsmokers. The death rate from coronary artery disease among the regular smokers of cigarettes is about 1.5 that of nonsmokers. Pipe smokers appear to engage in this habit with comparative impunity.

This problem is a difficult medical challenge, for it involves the mores of our social structure. If it is positively proved (and evidence points in this direction) that smoking is a prime causative factor in bronchogenic carcinoma, one of the greatest causes of cancer could be eradicated.

**Nicotine and smoking.** The importance of nicotine in tobacco smoke has been the subject of much investigation. So-called denicotinized cigarettes, containing about 40 per cent of the normal nicotine content, are readily available. Johnston (1942) experimented with a series of smokers by giving them a hypodermic injection of nicotine instead of a smoke. Smokers thought the injection pleasant and found that it served as an adequate substitute for a smoke. Nonsmokers experienced the sensations from the nicotine injections as "queer." In lieu of smoking Johnston administered 80 doses of nicotine, 1.3 mg. subcutaneously, to himself. These doses were given several times a day, and he preferred the injection to cigarette smoke inhalation.

Finnegan *et al.* (1945) compared the reactions of 24 habitual smokers to cigarettes of normal and of negligible nicotine content. Their conclusions were strikingly different. These investigators found nicotine an unimportant factor with many individuals in the cigarettes that they were given to smoke. Others felt the lack of nicotine in the tobacco. There was no correlation between the number of cigarettes smoked daily by the individual and his dependence upon nicotine. The factor appeared to be entirely personal. Finnegan *et al.* state: "Even in individuals in whom nicotine becomes a major factor we feel that a cigarette containing no nicotine would be grudgingly accepted as better than no cigarette at all."

The personal equation here again becomes manifest as the important issue. Apparently in some individuals smoking is a residue of the infantile habit of sucking. In others the nicotine absorption appears to play a role in their sense of well-being and tranquilization.

Most domestic American cigarettes are made from blends of several types of tobacco which differ in chemical composition and in the qualities, such as taste and aroma, which they impart to the smoke. The finished blends from which most American cigarettes are made generally contain about 1.7 per cent nicotine. Cigar and pipe tobaccos contain around 1.5 per cent of the alkaloid.

In the smoking of cigars and cigarettes, the unburned portion of the tobacco acts to absorb or filter out some of the nicotine and other condensable materials from the smoke stream; hence the closer to the end the cigarette or cigar is smoked, the shorter will be the filtering tobacco column, and the greater will be the concentration of these condensable materials in the smoke. Filter cigarette holders containing silica gel, activated charcoal, or another cigarette have been used to reduce the amount of smoke condensate and nicotine which the smoker receives, but today the filter-tip cigarette is more popular. The filters employed on most filter-tip cigarettes consist of creped paper or plugs of tightly packed cellulose acetate fibers. Some contain, in addition, activated charcoal to enhance their effectiveness, particularly in removing constituents which exist in the vapor phase of the smoke.

Smoking an average unfiltered cigarette in a normal fashion, the smoker receives about 1.5 to 2 mg. of nicotine, a part of which will be absorbed into the body. The cigarettes of some popular filter-tip brands may yield as little as 1 mg. or less of nicotine to the smoke. The quantity of nicotine obtained in the smoke is influenced by the speed with which the cigarette is smoked, that is, by the volume and frequency of the puffs. By taking larger puffs at more frequent intervals, more of the nicotine in the tobacco is transferred to the mainstream smoke. The moisture content of the tobacco also affects the amount of nicotine transferred to the smoke, more nicotine being obtained from drier cigarettes or cigars.

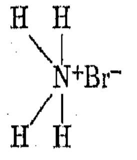
Many smokers inhale the tobacco smoke into the lungs, and others allow it to remain in the mouth and expel it through the nostrils and mouth. It is obvious that inhalation promotes the absorption of nicotine; prolonged contact with the membranes of the lungs provides excellent opportunity for nicotine absorption. Greenberg *et al.* (1952) demonstrated that only a small fraction of the nicotine in the smoke of cigars or cigarettes is retained in the bodies of smokers who do not inhale. With inhalation, nearly all of the nicotine is absorbed. Haag and Larson (1942) observed that those individuals who inhale tobacco smoke excrete about 10 times as much nicotine in the urine as those who do not inhale the smoke. This appears to be a faithful criterion of the total nicotine absorbed, for Finnegan *et al.* (1947b) showed that the quantity of nicotine excreted by the dog was a linear function of the dose.

One of the harmful effects of tobacco is due to nicotine absorption. This can be diminished by the use of low nicotine tobaccos, avoidance of inhalation of the smoke, and the use of filters and holders for cigarettes as condensers for the nicotine and tars.

In a report of the Royal College of Physicians of London on smoking in relation to lung cancer and other diseases (1962), the following comments are of interest. It appears advisable to reduce the nicotine content and tars of the tobacco used in the making of cigarettes. Filter tips are advantageous in the reduction of tars and nicotine that appear in the smoke. However, it will take years to assess accurately the effect of these measures in reducing the harmful effects of smoking.

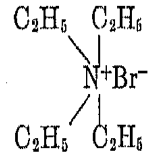
### QUATERNARY AMMONIUM COMPOUNDS

The quaternary ammonium compounds chemically may be looked upon as ammonium chloride or bromide in which the 4 hydrogen atoms have been replaced by alkyl groups as follows:



$$\begin{array}{c} \mathrm{H\quad H} \\ \mathrm{N^+Br^-} \\ \mathrm{H\quad H} \end{array}$$

Ammonium Bromide



$$\begin{array}{c} \mathrm{C_2H_5\quad C_2H_5} \\ \mathrm{N^+Br^-} \\ \mathrm{C_2H_5\quad C_2H_5} \end{array}$$

Tetraethyl Ammonium Bromide

In aqueous solutions quaternary ammonium compounds ionize, as does ammonium bromide. They form negative bromide ions and stable positive substituted ammonium ions. Their pharmacologic response is produced by the positive ion.

In 1869 Brown and Frazer observed that compounds with this general structure evoked a response on skeletal muscle similar to that of curare. This action, for the most part, is independent of the character of the alkyl groups attached to the nitrogen atom in the molecule.

In addition to their curare-like action, these substances elicit a stimulating response on the peripheral cardiac vagus, slowing the heart in a manner similar to that of muscarine and pilocarpine.

Another striking response of these agents is their capacity to mimic the action of nicotine on autonomic ganglia. These ganglia are first stimulated, then paralyzed. It is this effect which has made these substances valuable in clinical medicine. Burn and Dale (1915) demonstrated that some of the quaternary ammonium compounds did not elicit the cholinergic action or the incipient autonomic ganglionic-stimulating action of nicotine but produced only the paralyzing ganglionic effect of nicotine.

### Tetraethylammonium Chloride (Etamon Chloride).

Etamon chloride is available for clinical use principally in the treatment of peripheral vascular disease. It is provided in aqueous solution (100 mg. = 1 ml.) for intravenous and intramuscular injection. The intravenous dose is 2 to 5 ml., not to exceed 7 mg./kg., however. The intramuscular dose is 10 to 12 ml. (5 to 6 ml. in each buttock) not to exceed 20 mg./kg. The frequency of administration is dependent upon the relief afforded. Usually 1 to 2 injections daily have been given.

Acheson and Moe (1946) and Acheson and Pereira (1946) have extensively studied the effects of Etamon on the circulation. They showed that in tolerated doses Etamon blocked the autonomic ganglia, effecting inhibition of structures innervated by the autonomic nerves. The intravenous administration of the drug in laboratory animals obliterated the response of the nictitating membrane to stimulation of the preganglionic fibers. Stimulation of the postganglionic fibers in the Etamonized animal evoked a normal response. This ganglionic action was demonstrated also with respect to the extrinsic nerves of the heart.

Through its autonomic ganglionic action Etamon was shown to interrupt gastrointestinal motility and to diminish the volume and acid content of gastric secretion.

Stone *et al.* (1951) showed that Etamon, when injected into the blood supplying the adrenal glands of cats (with restricted circulation), caused definite pressor responses and contraction of the nictitating membrane. When the compound was injected into the jugular vein, these results did not prevail. They concluded that Etamon under these conditions evoked the secretion of epinephrine and norepinephrine from the adrenal medulla.

**Toxicologic phenomena.** Etamon is a powerful pharmacologic agent and must always be used with much discretion. The toxic effects are prompt, and in dogs death results from respiratory failure. If the shock of the administration (the ganglionic blocking) is tolerated, the subsequent toxicologic effects are minor. This is illustrated by the intravenous injection of the drug in dogs. In 19 animals 30 mg./kg. produced no deaths, but 36 mg./kg. was the $LD_{50}$ of Etamon upon intravenous injections.

Therapeutically equivalent doses administered repeatedly to dogs, mice, and rats produced no significant effects on the kidneys, spleen, and other visceral organs.

**Absorption and excretion.** Etamon is poorly absorbed from the gastrointestinal tract. Indeed, in man, only 5 to 15 per cent of the compound is absorbed upon oral administration. Absorption is prompt from the depots of intramuscular injection.

Etamon is promptly excreted by the kidneys and appears in the urine unaltered by cellular metabolism.

**Therapeutic uses.** The principal uses of Etamon are listed below.

1. Etamon has been chiefly used in the treatment of *peripheral vascular disease.* The treatment is directed towards the restoration of the patency and normal caliber of the involved blood vessels. Accordingly, Etamon has found application in the treatment of *Buerger's disease, Raynaud's disease,* and *thrombophlebitis.* Although the cases reported are not numerous, Etamon was found to afford varying degrees of relief in most cases. Since the drug affects the ganglia of the adrenergic nerves to the blood vessels, it is natural that success should be more striking when the reduced blood supply is mainly due to vascular spasticity rather than to obliterative structural changes. Success has also been reported with Etamon in the treatment of *causalgia.*

2. Hirshleifer *et al.* (1952) used Etamon in *coronary artery disease* with pain. They observed in all of their 23 cases a relief of pain and a diminution in the number and severity of the attacks. The drug was administered intramuscularly in doses of 300 to 500 mg. daily for 3 days, and then adjusted to a biweekly or weekly basis. It is their opinion that Etamon warrants a definite place in the treatment of coronary patients with intractable pain who have not responded to treatment with the usual therapeutic measures.

3. Etamon has been used with some degree of success in the treatment of *angina pectoris.* Atkinson (1950) used Etamon in 28 cases of angina pectoris. Beneficial results were obtained in 25, as demonstrated by fewer attacks and a greater exercise tolerance. Etamon is recommended by Atkinson in cases of angina pectoris where other methods of treatment have proved to be inadequate.

4. Etamon has been used by Jonez (1953) to provide peripheral vasodilatation in *multiple sclerosis.* The drug at best appears to provide only a palliative treatment and is most helpful in the acute stage of the disease.

Patients receiving Etamon must be kept in a recumbent position for at least 1 hour after the injection to avoid postural hypotension. In certain patients to whom Etamon has been given, the capacity to void or defecate is temporarily lost. This untoward side effect is not a frequent finding.

Epinephrine and neostigmine have been found useful in controlling untoward or excessive vascular actions of Etamon.

Etamon appears to have a place in the physician's armamentarium in the treatment of peripheral vascular disease. Its action, however, involves all autonomic ganglia, the parasympathetic as well as the sympathetic. The action of the drug therefore involves many structures in addition to the ganglia of the adrenergic nerves to the blood vessels. The most valuable and specific drugs for the treatment of peripheral vascular disease are adrenergic peripheral blocking agents of the tolazoline type, rather than a ganglionic paralyzant.

In an extensive review of the pharmacology and clinical application of ganglionic blocking agents, Moe and Freyburger (1950) state: "Ganglionic blocking agents may have a limited field of usefulness in the human subject, but it may develop that their chief value lies not in answering questions, but rather in posing them."

### Hexamethonium Chloride.

This compound is a ganglionic blocking agent. Since it is used principally in hypertension, it is discussed with other similar agents on page 685.

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# PART VI

## THE PHARMACOLOGIC RESPONSES OF THE HEART AND CIRCULATION

## 39

## *General Consideration of the Pharmacologic Responses of the Heart*

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In the foregoing sections of this treatise we have considered the responses of the central nervous system and the autonomic nervous system to the action of drugs. It was observed that the central nervous system is sensitive to the presence of many different types of drugs and that the stimulants and depressants of this system constitute one of the largest classes of pharmacologic agents. Many of these agents indirectly affect the heart and circulation. For example, the adrenergic drug norepinephrine depresses the heart rate through vagal stimulation. The anesthetic cyclopropane sensitizes the heart to the action of epinephrine. Furthermore, in our study of the drugs affecting the autonomic nervous system we learned that many agents of this class produce cardiac effects through their actions on the extrinsic nerves of the heart.

In this section our prime consideration will be the responses which are elicited by drugs on the heart, blood vessels, blood, and the hematopoietic system. Many of these effects, as previously mentioned, are mediated through the nerve supply to the heart. Other responses are elicited by the action of pharmacologic agents on the nerve supply to the blood vessels, producing constriction or dilatation.

Certain drugs directly affect the heart muscle with a considerable degree of specificity. For example, digitalis exerts its principal action directly on the myocardium, increasing the force of contraction. Other drugs act directly upon the musculature of the blood vessels independent of their innervation and cause dilatation, such as the nitrites, or constriction, such as posterior pituitary solution.

In addition, in this section we shall consider drugs which stimulate the hematopoietic system, such as vitamin $B_{12}$, and those which depress it, such as radioactive phosphorus. The drugs which prolong the clotting time of blood, heparin and bishydroxycoumarin, will be discussed, along wit vitamin K, which diminishes the clotting time of blood.

As the heart is the central organ of the circulation, our discussion will begin with it. We will review certain physiologic principles of heart action upon which the rational treatment of cardiac disease with drugs is based.

### Physiologic Aspects of the Heart

**The heart as a pump.** The sole function of the heart is to serve as a pump. It propels the blood through the arteries to the various organs of the body. As a muscle the myocardium possesses the unique property of undergoing continuous activity. On the average, in a person who lives his 3-score years and 10, the heart has beat 2500 million times without a full second's relaxation.

Each ventricle produces an output of blood of about 70 ml. at each beat. This may be doubled during vigorous exercise. The *minute volume* of the heart is the amount of blood pumped at each beat multiplied by the number of beats per minute. If the left ventricle pumps out 70 ml. per beat and the pulse rate is 70 per min., the minute volume would be 4.9 L.

The period of complete circulation of the blood is short. In the human being it has been calculated that a single corpuscle may start at the right atrium, travel the paths of the pulmonary and systemic circulations, and return to the right atrium in 60 seconds. Thus it requires approximately 70 heart beats to accomplish complete circulation.

**The work of the heart.** The heart, blood, lungs, and blood vessels may be considered as an integrated physiologic system whose function it is to supply oxygen to the tissues and remove carbon dioxide. To be sure, there are many other substances carried to the tissues by the blood, but oxygen is the most critical. It is well known that cerebral hypoxia will produce unconsciousness within a period of 5 to 10 seconds, and therefore the work of the heart in supplying oxygen to the tissues is vital for the maintenance of tissue metabolism and life. Because the efficiency of the functioning of various tissues is dependent upon their receiving an oxygen supply adequate to meet various functional needs, the control of cardiac output is safeguarded by a series of protective reflexes. For example, an athletic individual at rest may consume 0.25 L. of oxygen per min. with a pulse rate of 70. When engaged in active exercise, his oxygen consumption will increase to 3 L. and his pulse rate to 165. Thus the oxygen consumption increase is 12-fold. Simultaneously the cardiac output in L./min. increases from 5 to 25. Therefore the stroke volume increase is from 70 ml. to 150 ml. The heart pumps more than a million gallons of blood per year.

**Cardiac automaticity.** The heart enjoys the inherent capacity to contract rhythmically. It is independent of the nerve supply to the heart and continues after the severance of the extrinsic nerves or their blockade with drugs. Fragments of cardiac muscle that have been grown in tissue culture show rhythmic contractility.

The wave of cardiac excitation begins at the sino-atrial node and passes through the atria and ventricles. The excitatory wave spreads from the S-A node through the atrial tissue at the rate of about 1 meter per second. The impulse is transferred to the atrial-ventricular node (A-V) and from here is transmitted through the special tissue known as the *bundle of His*. The excitatory wave is conducted through the ventricular walls from the bundle of His by means of the bundle branches and the Purkinje fiber network. These are atypical muscle fibers that resemble embryonic heart tissue. These fibers pass down the right and left ventricles, one on either side of the ventricular septum. They are obscured by the endocardium.

The wave of excitation of the myocardium is sufficiently intense to produce an action current in the skin, which is measurable by means of a galvanometer. Electrocardiographic recordings measure this excitatory wave.

The S-A node is referred to as the *pacemaker*. When it is destroyed, cardiac activity is greatly diminished or stopped momentarily. Temperature changes in the S-A node of an isolated beating heart effect a change in the cardiac rate. Similar changes in temperature in other portions of the heart do not affect the rate. If the S-A node is transplanted to other areas of the heart, it will continue to function as the pacemaker.

The wave of excitation that passes over the heart initiates the atrial and ventricular beats. After the retreat of the electrical impulse the myocardium enjoys a *refractory period*. During this period the muscle is undergoing metabolic and physical changes, preparing itself for the next systole. The heart is refractory to stimuli reaching it during this period. The refractory period lasts about 0.3 second. With a pulse of 100 per minute, the refractory period is reduced to 0.2 second.

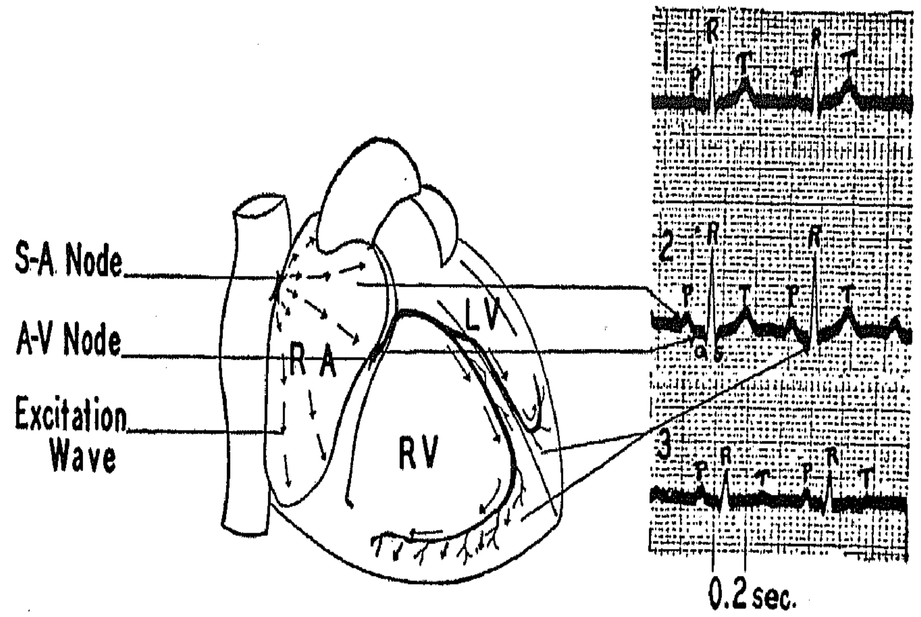

Fig. 39-1. Electrocardiogram, Leads I, II, and III, with diagram of heart showing the origin of the waves schematically. (From Bard, *Macleod's Physiology in Modern Medicine*, C. V. Mosby Company, St. Louis, 1941.)

The cardiac rhythmicity may be altered by disease. Under disease conditions alterations in the refractory period, excitability, and propagation rate may occur in such a way that the excitatory waves are self-perpetuating. If this process of self-stimulation is well organized, a very rapid atrial rate (around 300 per minute) may result. This is called *atrial flutter*. In other cases, or at other times in the same patient, this activity may become disorganized, producing random activity of the component fibers. This totally ineffectual and arrhythmic activity is called *fibrillation*. *Cardiac arrhythmias* are of special pharmacologic interest because of the availability of such drugs as digitalis and quinidine to treat the condition effectively.

**The electrocardiogram.** The cardiac excitatory wave is demonstrable in detail by means of the action current referred to the skin. Measurement of this current is accomplished by means of the electrocardiograph. By attaching electrodes to the arms and left leg, or to various predetermined areas of the chest, and recording the cardiac action currents on a galvanometer, oscilloscope, or oscillograph, the cardiac cycle may be traced in great detail. The record is of great value in diagnosis and has special pharmacologic interest because many drugs effect changes in cardiac rhythm. In addition, the salutary effect of digitalis and quinidine in the treatment of cardiac arrhythmias is most convincingly demonstrated by electrocardiographic changes.

For convenience, figure 39-1 has been included to show the relationship between the excitatory cardiac wave of the myocardium and its representation on the electrocardiogram.

**Characteristics of the heart muscle.** The physiologic principles which govern the activity of the heart muscle are of importance in the consideration of the action of drugs on the heart. First, the heart obeys the "All or None Law." This is exemplified by the observation that if the myocardium undergoes contraction at all, it will contract to its maximal limit. Second, after the contraction of the heart muscle, there is a refractory period during which the muscle does not respond to stimuli. This has been discussed previously. Third, although much experimental evidence has shown that increased myocardial contractile energy results when the heart is dilated (Starling's law of the heart), there is no evidence to show that the normal heart actually adjusts to increased circulatory demands by dilatation, as was previously thought. On the contrary, the heart actually gets smaller during exercise. It appears that the normal adjustments of the heart to exertion, or even to psychologic states related to exertion, are mediated via the autonomic nervous system from centers located in the hypothalamus. These same centers also control the tone of arterioles and venous reservoirs so that the entire circulatory system adjusts to these requirements synchronously. Fourth, the myocardium does not enjoy a capacity for anaerobic metabolism, as does skeletal muscle. It cannot run into an oxygen debt but must have a constant and generous oxygen supply. This is ac-

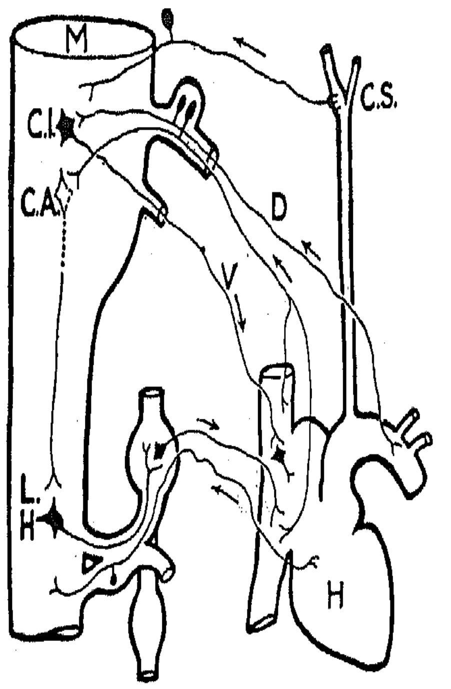

FIG. 39-2. Simplified diagram of the nerve supply of the heart. *C.I.*, cardio-inhibitory center; *C.A.*, cardio-accelerator center; *M*, medulla oblongata; *L.H.*, lateral horn of spinal cord; *D*, depressor fiber (afferent vagal); *V*, efferent vagal fiber; *C.S.*, carotid sinus; *H*, heart.

(From G. H. Bell, J. N. Davidson, and H. Scarborough, *Textbook of Physiology and Biochemistry*, The Williams & Wilkins Company, 1961.)

complished by the circulation of the blood through the coronary vessels.

**The coronary circulation.** The myocardium is supplied with blood from the left and right coronary arteries. They arise directly from the aorta adjacent to its origin. The heart enjoys a very rich capillary supply. The oxygen consumption of the heart is greater per gram than that of any other tissue. Therefore, its blood supply must be abundant. Indeed, approximately 20 per cent of the entire output of blood from the left ventricle may pass through the coronary circulation to nourish the heart itself. The oxygen supply, and hence the blood supply to the heart through the coronaries, must vary to meet changing conditions of activity of the individual. It has been stated that the myocardium cannot accumulate an oxygen debt. Its functional activity is dependent from moment to moment upon the adequacy of the oxygen supply from the coronary circulation.

It becomes apparent that the efficiency of cardiac output is responsible for supplying oxygen and nourishment to the heart itself; therefore incipient heart failure not only embarrasses the general circulation but diminishes the blood supply to the heart muscle, further reducing its efficiency. The vicious circle obviously can start in the coronary vessels. If these fail to dilate in emergencies; the heart experiences hypoxia, producing poststernal pain, and thus circulation may become embarrassed as a result of insufficient nourishment. The latter condition is seen in angina pectoris and in coronary occlusion.

To relieve cardiac hypoxia in angina pectoris, the promptly-acting vasodilator glyceryl trinitrate is available.

**The extrinsic nerves of the heart.** The vagus nerve is the cardiac inhibitor. Vagal stimulation produces cardiac slowing and ultimate cardiac arrest. In mammals the vagus nerve exerts its slowing effect upon stimulation by its action on the atria and the junctional tissues. The vagus nerve has no direct action on the ventricles. In vagal standstill the heart is engorged with blood in diastole. The cardiac inhibition of the vagus can be demonstrated in man by administering large doses of atropine. When the vagus activity is obliterated, the pulse rate will increase to about 160 per minute.

The sympathetic nerve supply to the heart functions as a cardiac accelerator and hence reciprocates with the vagus. By stimulation of the cardiac accelerator nerve, the heart rate is increased, the force of contraction of the atria and ventricles is increased, and conduction from the atria to the ventricles is accelerated. We have observed previously (see page 541), that the injection of epinephrine elicits this type of cardiac response. Figure 39-2 shows the innervation of the heart by the extrinsic nerves.

**Reflex mechanism of cardiac activity.** The activities of the cardiac inhibitor and accelerator nerves are correlated in the vagus center and cardiac accelerator center, respectively. These centers are constantly receiving impulses from various structures of the body such as the hypothalamus, or from the heart itself. It is well known that trauma to the intestines will reflexly stimulate the vagus center and produce cardiac inhibition. Furthermore, the stimulation of the sciatic nerve will cause a change in pulse rate. Usually the rate is accelerated.

The cardiac vagus also contains afferent fibers. The receptors of these fibers lie in the atrial tissue and the aortic arch. An increase in the blood returned to the right atrium by the vena cava distends the right atrium. The vagal receptors beneath the endocardium and in the walls of the great veins near the right atrium are stimulated. The afferent vagal fibers carry impulses to the vagal center, which cause efferent vagal depression and cardiac acceleration.

**Carotid sinus reflexes.** It was established many years ago that a rise in arterial blood pressure stimulated the vagus and caused cardiac slowing (Marey's law). This reflex was formerly presumed to have its origin in the vagal receptors in the aortic arch. It was demonstrated that the reflex mechanism also involved the *carotid sinus*. The carotid sinus is an enlargement of the common carotid artery where it bifurcates into the internal and external carotids. The sinus contains afferent nerve receptors from a branch of the glosso-pharyngeal nerve. The stimulation of this nerve causes reflex slowing of the heart and a fall in blood pressure. The carotid sinus nerves function in a manner similar to the afferent vagus fibers. Pressure in the sinus caused by an increase in blood pressure reflexly causes cardiac inhibition through the vagus center and a subsequent fall in blood pressure. This is accomplished by the central connection of the sinus nerve with the vagus and vasoconstrictor centers. The carotid sinus is also connected by nerve fibers to the superior cervical sympathetic ganglion.

Many drugs, such as digitalis, produce some of their effects upon the heart reflexly through the carotid sinus mechanism.

We shall now turn our attention to drugs which affect the force of contraction of the heart and cardiac rhythm.

# 40

# *The Response of the Myocardium to Digitalis*

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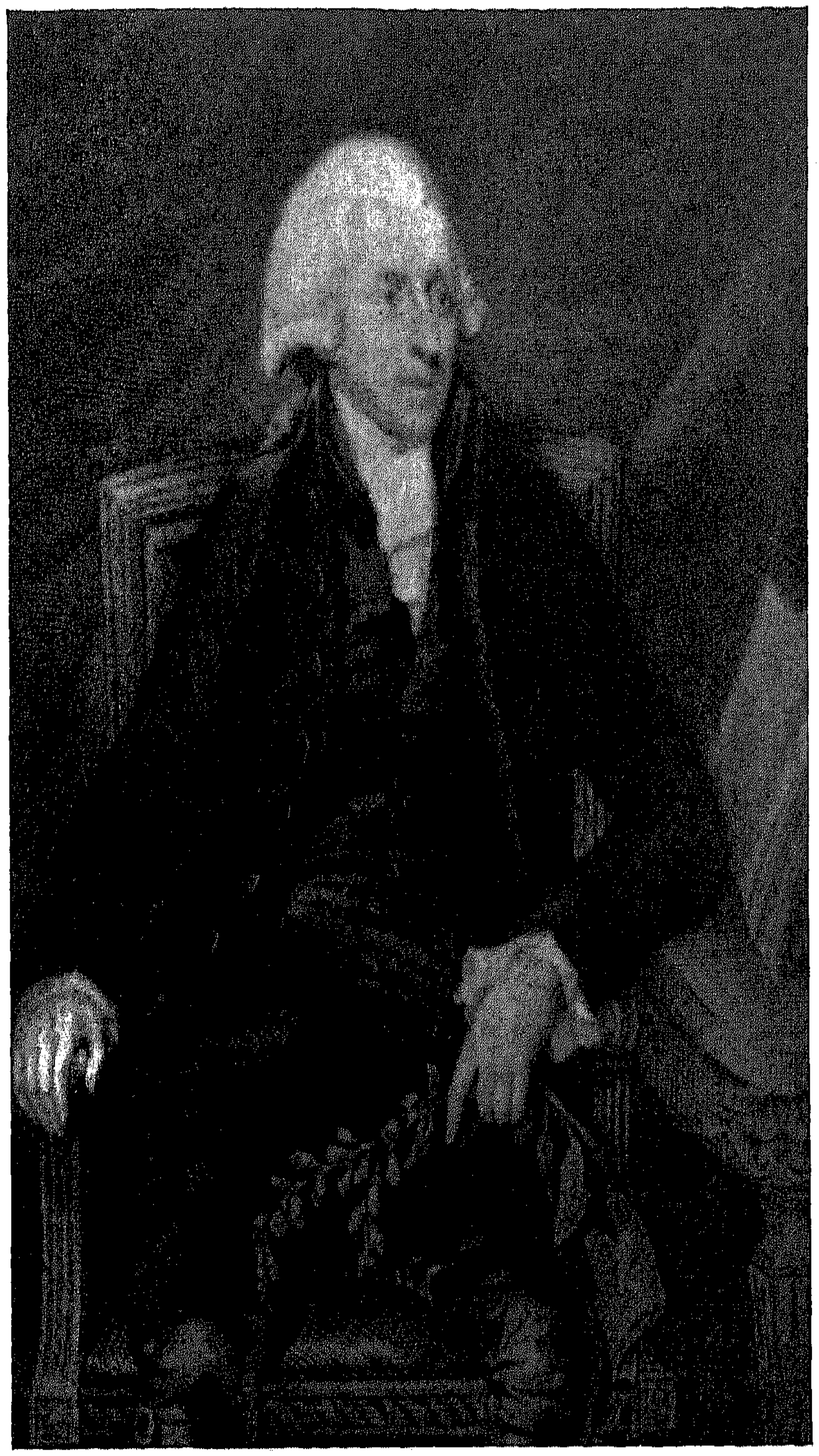
In the treatment of congestive heart failure with or without atrial fibrillation digitalis is the drug of choice. There is no substitute for digitalis or its glycosides in the treatment of this condition. Looking back over an ever-lengthening past of therapy with vegetable drugs, digitalis stands today as one of the most dependable and useful of all of the vegetable drugs.

**The introduction of digitalis into medicine.** There is no more fascinating story in the annals of medical history than that which describes the discovery of the medicinal usefulness of digitalis. Digitalis was mentioned first as a medicinal substance by the Welsh physicians of the thirteenth century. In 1542 Fuchs assigned to it the botanical name *Digitalis purpurea.* This name was fittingly chosen because of the likeness of the flower to a finger and because of its purple pigmentation. The common name of the plant *foxglove* is said to be a corruption of the descriptive name *folk's glove.* The principal medicinal use of the plant at that time was as an emetic. Parkinson in 1640 referred to the plant as evoking expectorant and emetic actions. Indeed, for this purpose it was mentioned in many of the provincial formularies. Employed in this manner the drug was not reliable, and its use soon diminished.

The modern use of digitalis, the purple foxglove, in medicine stems from the classical observations of William Withering toward the end of the eighteenth century. Withering was a busy practitioner of Birmingham, England. In 1776 it is said that he was treating personally 2000 to 3000 indigent patients a year. He was an able botanist, a mineralogist of repute, and widely sought as a medical consultant. Benjamin Franklin sought his advice on the treatment of urinary calculi.

Out of this busy life Withering, frail of body but keen of intellect, was called to a place of fame in the annals of medicine. The events are recorded by Wilkinson (1950).



WILLIAM WITHERING
1741–1799
*The discoverer of the use of the foxglove in the treatment of dropsy*
"That digitalis has the power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends."

In 1775 he was asked about a family recipe for the cure of the dropsy, and was told that it had been kept as a family secret for many years by an old Shropshire woman who had sometimes made cures when more regular practitioners had failed. The medicine contained twenty different herbs and was said to produce vomiting and purging. Withering said that it was not difficult for one conversant in these subjects to perceive that the active plant could be none other than the foxglove. It is startling to learn that a botanist in 1775 knew enough pharmacology to detect the active ingredient in an herb tea. He tried it out on his free patients, and was especially encouraged when Dr. John Ash told him that Dr. Crawley, principal of Brazen Nose College, had been cured of a hydrops pectoris by digitalis root, but as a biennial plant is unlikely to have a uniformly active root. Withering used the leaves and gathered them when the plant was in flower, because he found that they varied in dose if gathered at other seasons. At first he used a decoction, but in order to obtain more accurate dosage turned to an infusion and finally preferred the dried leaf. In 1785, after using the medicine for ten years, he published his *Account of the Foxglove*.

This event in medical history has been beautifully depicted in the charcoal drawing by E. L. Chase and later in oil by Bell. It is entitled "Golden Sovereigns for the Secret of the Wayside Flower."

From this work one can detect the keenness of observation that Withering exercised when he recorded, "It has power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends." Again he declared, "The most frequent sign of too much digitalis is nausea and vomiting, and when occurring they indicate the cessation of the drug." Withering's original directions for the use of digitalis (1783) were exacting. "Let the medicine be continued until it acts on the kidneys, the stomach, the pulse, or the bowels: let it be stopped upon the first appearance of any one of these effects."

Withering believed the drug to be mainly a diuretic and hence its value in dropsy. The finer pharmacologic responses to digitalis were only vague to him, although against the background of his time his work was a paragon of clinical medical observation.

In 1800 John Ferriar after studying the action of digitalis wrote, "Extractions from the leaf furnish us a means of regulating the pulse to our wish and supporting it in a given state of velocity as long as we may judge it proper." One year later Kinglake recognized the increased stroke volume of the digitalized heart.

For more than a century digitalis was believed to contain diuretic and cardiac principles. The diuretic principles presumably were extracted by water, and the infusion of digitalis was used in edema other than that of cardiac origin. The tincture containing a high alcoholic menstruum was used in congestive heart failure and arrhythmias. In 1911 the distinguished English clinician, Sir James Mackenzie, and the pharmacologist, A. R. Cushny, elucidated the action of digitalis. They attached electrodes to the beating atria of the heart of a dog. By means of a mild tetanizing current they disturbed the atrial rhythm and produced a condition comparable to the clinical picture of atrial fibrillation. This disordered atrial rhythm affected the beat of the ventricles. Their beat became rapid and less effective. Digitalis was given, and the tetanizing current was continued. The atria continued in their state of fibrillation. But the ventricles no longer were affected by the arrhythmia of the atria. The ventricular beat was slowed and soon became more effective. Digitalis blocked the A-V node.

The work of Mackenzie and Cushny stands alongside of that of Withering in elucidating the action of digitalis. This experiment today is the centerpiece of our knowledge of the action of digitalis. However, we have woven a great deal of embroidery around this centerpiece in recent years.

Another milestone in the advance of digitalis therapy is attributed to the clinician Wenckebach (1910). It was he who observed the value of quinine in atrial fibrillation. In his studies with digitalis he emphasized the extraordinary value of the drug in cardiac decompensation when the condition is not accompanied by a disordered cardiac rhythm.

Laquer (1940 *et seq.*) succeeded in obtaining the glycoside digitoxin in quantities to permit extensive clinical trial. Laquer supplied Gold with samples of pure digitoxin for clinical trial. Gold *et al.* (1938 *et seq.*) included in their studies also the glycosides from *Digitalis lanata*. These investigations were responsible for pointing out fine differences in the quantitative pharmacologic responses. And finally, the work of this group showed the value of crystalline "digitoxin" as a stable, dependable, and orally available digitalis glycoside.

**Digitalis leaf and glycosides.** The United States Pharmacopeia recognizes only *Digitalis purpurea*, although it recognizes also glycosides of *Digitalis lanata*. Digitalis is defined as "the dried leaf of *Digitalis purpurea* Linné (Fam. Scrophulariacea)." One-tenth gram of the drug is equivalent to 1 U.S.P. Digitalis Unit.

The glycosides of *Digitalis purpurea* and *lanata* are similar in chemical constitution and also in their qualitative pharmacologic response. *Digitalis purpurea* contains 3 well-known glycosides. They are: (1) digitoxin, (2) gitoxin, (3) gitalin. The last named is likely a mixture of several glycosides. By far the most important of these is digitoxin. There is also a saponin present in the drug known as *digitonin*. There are many other glycosides present in the digitalis leaves of *D. purpurea* and *D. lanata*. At least 20 of these glycosides have been isolated and their structures identified. Apart from digitoxigenin, gitoxigenin, digoxigenin, gitaloxigenin, and diginatigenin, no new aglycones have been found. As gitatoxigenin is the 16-formyl derivative of gitoxigenin, the aglycones of the cardiac digitalis glycosides comprise 4 basic forms which differ from each other with respect to the number of hydroxyl groups (table 40-1). The great variations are thus mainly due to the structure of the sugar chain (Stoll, 1959). Preliminary pharmacologic tests were conducted on many of these rarer glycosides by Henderson and Chen (1962).

The relationship between the glycosides of *D. purpurea* and *lanata* may be observed from table 40-2, which is a condensation of an elaborate chart of the glycosidal relationship devised by Stoll (1937).

From *D. purpurea* the United States Pharmacopeia recognizes only the principal glycoside "digitoxin." From *D. lanata*, digoxin and deslanoside are official and also the native glycoside "lanatoside C" from which digoxin is derived is official in the National Formulary.

**Chemistry of the digitalis glycosides.** The cardiac glycosides of digitalis are typical glycosidal structures, *i.e.*, upon hydrolysis they decompose into their *genins* or *aglycones* and split off their sugar molecules. Thus, digitoxin upon complete acid hydrolysis yields 3 molecules of *digitoxose*, a reducing monosaccharide with the empiric formula $C_6H_{12}O_4$. In the *purpurea* leaf, Stoll (1937) has shown that digitoxin exists as "*Purpurea Glycoside A*" which has an analog in the *lanata* leaf, for lanatoside A is an acetyl derivative of purpurea glycoside A. Mild hydrolysis of lanatoside A yields acetic acid, converting it into purpurea glycoside A. Enzymic hydrolysis of purpurea glycoside A yields glucose and digitoxin. This is shown in the following diagram.

1. Lanatoside A by mild alkaline hydrolysis yields
↓
2. Deacetyllanatoside A + acetic acid
(Purpurea Glycoside A) upon enzymic hydrolysis yields
↓
3. Digitoxin + 1 mole of glucose upon complete acid hydrolysis yields
↓
4. Digitoxigenin + 3 moles of digitoxose

TABLE 40-1

*Chemical Formulas of the Genins of the Principal Cardiac Glycosides*

| | C-12 | C-14 | C-16 |
|---|---|---|---|
| Digitoxin....... | | OH | |
| Gitoxin......... | | OH | OH |
| Gitalin.......... | | OH | OH |
| Digoxin......... | OH | OH | |

The genins of the cardiotonic glycosides are complex structures. There are only minor differences chemically among the various genins. This is shown in table 40-1, using the formula of digitoxigenin as a pattern and the substituent hydroxyl groups at various positions. The hydroxyl group on position 3 may be either *cis* or *trans* to the carbon atom of the methyl group at position 10. It is generally *trans*. The principal cardiotonic genins differ from each other by the stereochemi-

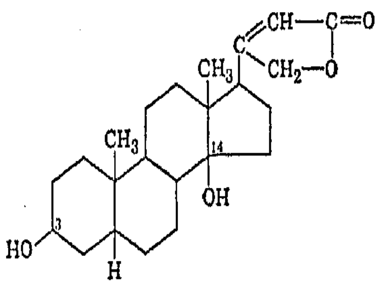
TABLE 40-2

*Interrelationship between Digitalis Purpurea and Digitalis Lanata Glycosides*

(Stoll, 1937)

| DIGITALIS PURPUREA | | | | DIGITALIS LANATA |
|---|---|---|---|---|
| *Native Glycosides* | | *Glycosides* | | *Native Glycosides* |
| Deacetyldigilanid A | ⟶ | Digitoxin | ⟵ | Digilanid A<br>(Lanatoside A) |
| Deacetyldigilanid B | ⟶ | Gitoxin | ⟵ | Digilanid B<br>(Lanatoside B) |
| Glycoside? | ⟶ | Gitalin Digoxin | ⟵ | Digilanid C<br>(Lanatoside C) |

From the chart it can be seen that *D. purpurea* and *D. lanata* yield the glycosides digitoxin and gitoxin; in addition, *D. purpurea* yields gitalin, and *D. lanata* yields digoxin. The glycosides exist in the plants as precursors called native glycosides, which upon partial hydrolysis yield the simpler glycosides indicated as shown.



Digitoxigenin

cal relationship of the ring structures and in the number of hydroxyl groups attached to the rings. These changes modify the cardiotonic activity quantitatively; the character of the response among the glycosides is essentially the same. For example, gitoxin with additional hydroxyl groups at positions 14 and 16 is from 40 to 60 per cent as active as digitoxin which has only the hydroxyl group at position 14. The stereochemical isomerism of the rings is the same in each of these genins. The unsaturated butyro lactone group seen in the genin is necessary for cardiotonic activity. When the double bond is removed by reduction with hydrogen the typical digitoxin action is lost. This unsaturated lactone linked to a favorable ring structure is essential for cardiotonic activity.

Chen *et al.* (1938) found that the genins of several of the cardiotonic glycosides including digitoxin exhibited qualitatively the same pharmacologic action as the corresponding glycosides. Quantitatively, the genins were less powerful and showed a lesser degree of persistence in action than the unhydrolyzed glycosides. The glycosides also are distinguished by a latent period before their action becomes manifest. Krayer (1944) observed a qualitative difference, however, between the action of digitoxin and its genin on the dog's heart. The genin produced an immediate and transient slowing of rate owing to central vagal stimulation. In equimolar quantities digitoxin was devoid of this action under the experimental conditions. The effect was observable by cross-circulation with an innervated heart-lung preparation. The compounds were administered to the blood supply of the central nervous system without their reaching the heart-lung circuit.

Chen and Henderson (1954), continuing work in progress for many years, studied 64 digitalis-like glycosides, aglycones, and their derivatives on etherized cats. Their comprehensive studies provided some general statements with regard to the correlation of structure and pharmacologic activity. Some of these relating to digitoxin are of special interest. For example, the *epimerization* of $C_3$ in the genin molecule of digitoxin forming 3-epi-digitoxigenin destroys cardiac activity. The removal of the hydroxyl group at $C_{14}$ is accompanied by a loss in activity as shown in the glycoside *resibufogenin.* Among the glycosides studied with a 5-membered lactone ring like digitoxin the order of activity generally followed the pattern of: trioside < bioside < monoside > aglycone.

The foregoing studies are indicative of the enormous amount of work which is in progress in attempting to unravel the mechanism of action of the cardiotonic glycosides.

### THE PHARMACOLOGIC RESPONSES TO DIGITALIS

**The response of the heart to digitalis.** The primary action of digitalis is on the heart. The action of the drug on the myocardium may be conveniently divided into 3 components. They are as follows:

1. Increasing the contractility of the heart muscle
2. Blocking of A-V conduction
3. Cardiac slowing direct and through vagal stimulation

*Digitalis increases the force of the systolic contraction in the dilated heart.* The stroke volume increase in the digitalized heart was observed first by Kinglake in 1801. The systolic shortening of the muscle fibers is greater and more prolonged. Hence the cardiac output is increased. There is also a more complete filling of the ventricles in diastole; this increases the force of ventricular systole by increasing the initial length of the muscle fibers.

The question of whether the increased contractility of the heart was produced directly or only indirectly through its action on conduction and slowing was answered by Cattell and Gold (1938). They used the papillary muscle of the right ventricle of the cat's heart. It was set up on an isometric lever and driven at a fixed rate. Its tension was measured photographically. When the papillary muscle began to fail *ouabain,* a cardiotonic glycoside, was added to the bath in concentrations which are available in therapeutics. These were as small as 1 to 75 million. Under the influence of the drug the tension rose and remained in that state for several hours. Cattell and Gold state, "No other chemical material is known which produces such definite and sustained increase in the systolic force of the mammalian heart muscle." A typical effect is seen in figure 40-1. It is concluded therefore that digitalis directly increases the force of contractility of the heart.

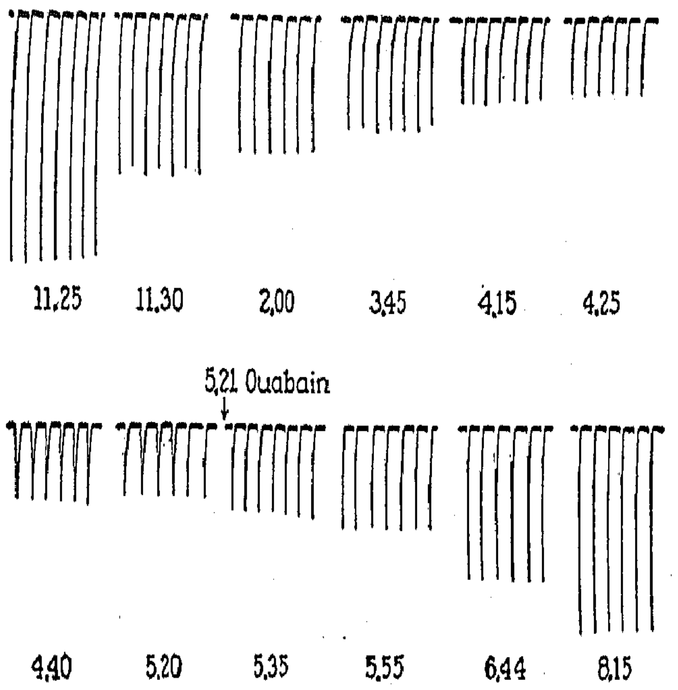


FIG. 40-1. Effect of cardiotonic glycoside on the systolic force of mammalian heart muscle. (From McK. Cattell and H. Gold: J. Pharmacol. & Exper. Therap., **62:** 116, 1938.)

Krop (1944) showed that epinephrine augmented the systolic force of contraction of mammalian cardiac muscle. The xanthine bases such as theophylline were ineffective in this respect except in concentrations not attainable in therapeutics.

The mechanism of action of digitalis in augmenting the contractile force of heart muscle has been the subject of numerous investigations. The importance of these studies is emphasized by the fact, that upon this action, the main value of digitalis in congestive heart failure depends. Furthermore, the elucidation of the mechanism of this response sheds light upon the series of events which are responsible for cardiac insufficiency.

Wollenberger and Karsh (1952) demonstrated the specificity of the cardiac glycosides for increasing the oxygen uptake in slices of the guinea pig's heart. For example, ouabain in concentrations of $3 \times 10^{-7}$ M afforded a maximal increase of 50 per cent in oxygen uptake with glucose or lactate as a substrate. Other tissues did not respond in a similar manner to ouabain. Peschel and Schlayer (1958) observed an increase of 12 to 19 per cent in oxygen uptake of rat heart slices with concentrations of ouabain $10^{-6}$ M. In other tissues this action did not prevail.

The stimulation of the oxygen uptake of tissue slices of the mammalian heart produced by digitalis is difficult to correlate with the beneficial action of the drug in congestive heart failure. First, the oxygen uptake of the tissue at rest is only a small fraction of the oxygen uptake of the muscle when it is engaged in the expenditure of energy. It is conceivable that the energy changes evoked in the tissue slice might be different qualitatively and quantitatively from those elicited in the contracting myocardium *in vivo.* Second, Bing (1958) showed that the oxygen consumption of the human heart in congestive failure is the same as that of the normal heart. Besides, the levels and utilization of the various metabolites of the cardiac tissue such as glucose, pyruvate and lactate are essentially the same in the failing and in the normal heart. Furthermore, the administration of lanatoside C did not effect a change in the oxygen consumption or the levels of the metabolites in the hypodynamic heart. It appears, therefore, that one must look beyond the *in vitro* acceleration of oxygen uptake by digitalis to account for its effect on the contractile mechanism.

Wollenberger (1949) demonstrated that the cytochrome system in cardiac tissue was not sensitive to ouabain. It was further shown that anaerobic glycolysis in heart slices was not affected by the cardiac glycosides. One must look further then into the effect of the glycosides upon the adenosine triphosphate (ATP-ATPase system) of energy transfer. The synthesis of ATP is a facet of the energy intake of the myocardium. Its breakdown by ATPase is a segment of the energy liberation by the heart.

Wollenberger (1947 and 1949) showed that the ATP and creatine phosphate concentrations in the failing heart in well-oxygenated heart-lung preparations are not diminished, nor are they augmented by the administration of the cardiac glycosides. If heart failure were associated with diminished ATP hydrolysis by ATPase, then the beneficial action of the glycosides should occur concomitantly with an increase of ATP hydrolysis and oxygen uptake and the expenditure of mechanical energy.

Feinstein (1962) studied the effect of ouabain on various constituents of the heart of the guinea pig in experimental congestive failure. The positive inotropic effect of the glycoside was shown not to be due to the capacity of the drug to increase high-energy phosphate levels in the failing heart. Feinstein interprets his experiments to indicate that steady-state levels of high energy phosphate compounds are not so important as their rates of synthesis.

If the rate of ATP breakdown were the limiting factor in the production of mechanical work of the heart and there were no defects in the contractile mechanism, digitalis would be ineffective in the treatment of congestive heart failure.

Although the energy uptake system of the myocardium appears to be essentially unaltered, as judged by the measurements one is capable of making in human congestive heart failure, certain experimental data must be considered. It was mentioned previously that the primary action of the glycosides of digitalis on this system was increased oxygen consumption. More recent work by Cherkes and Dmitrieva (1963) suggests that in various types of experimental myocardial insufficiency induced in the rat there are decreases in phosphorylase and aldolase activity and a diminution of glycogen content of the heart. These alterations were normalized by the administration of strophanthin. There may be similar changes in the human heart in congestive heart failure that one is not able to measure. Accepting our present knowledge as admittedly incomplete, it appears, however, that the basic defect in congestive heart failure is in *the energy utilization system of the contractile mechanism of the myocardium.* The primary action of digitalis is on this system; increases in oxygen uptake associated with the action of digitalis are in sequence to the primary action of increased work output by the heart. There appears to be clinical substantiation of these observations, since those types of congestive failure which result from a defect in free energy utilization or transfer of metabolic energy into mechanical work (chronic valvular or hypertensive heart disease) respond best to digitalis therapy.

It is well established that the cardiac glycosides and the calcium ion have synergistic actions. The cardiac glycosides mobilize the movement of calcium ions in cardiac muscle. The intracellular calcium level is increased. It is postulated that the glycoside makes available more ionic calcium by increasing membrane permeability, and therefore more of the cation is available to increase the contractile force of the beat. In addition, the calcium ion activates ATPase, which in turn would provide more energy from the concomitant breakdown of ATP. There is also evidence that the glycosides evoke a more favorable shift in $Na^+/K^+$ ratios toward the normal state in which the muscle fibers achieve their optimal contractility.

This ionic shift was formerly considered to be due mainly to an outflux of potassium ions. Work by Tuttle *et al.* (1962) using ouabain on the rabbit's atria failed to confirm this. They found at therapeutic levels the outflux of $K^{42}$ was equalled by the influx of $K^{42}$. In toxic concentrations the uptake of $K^{42}$ was blocked, which caused a net loss of the ion. They do not believe that the positive inotropic effect of the glycoside is associated with the fluxes of the potassium ion imposed upon the myocardium.

It is further possible that the glycosides of digitalis may directly affect the contractility of protein in addition to affording a more favorable cationic shift for contraction. For example, Waser (1957) showed that active cardiac glycosides caused an increased binding of potassium ions to actomyosin *in vitro.* Those glycosides, devoid of cardiotonic activity, failed to affect this property of actomyosin. More work will be needed to demonstrate specifically if this effect is associated with increased contractility and whether the diminution of potassium binding to actomyosin is a defect in the hypodynamic heart.

*Digitalis causes a partial blocking of A-V conduction.* Digitalis was observed first to diminish A-V node conduction by Mackenzie (1911). With Cushny (1911) he showed that in atrial fibrillation the impulses from the fibrillating atria no longer reached the ventricles after digitalization. The drug produces, therefore, a partial A-V block. Just how the glycoside acts on the conduction is not known.

The glycosides of digitalis depress conduction in the heart. There is a lengthening of the refractory period in therapeutic doses. The diminished conductivity is most marked in the A-V node.

The effect of digitalis on the refractory period of the different cardiac tissues is not uniform. Méndez and Méndez (1953) studied the effect of digitalis glycosides differentially on the atrial tissue, the atrial-ventricular propagation tissue, and the ventricles in the heart of the dog. When the atrial tissue maintained its vagal innervation, the glycosides decreased the refractory period of the atria. The refractory period of atrial-ventricular propagation showed a progressive increase until the glycosides produced complete A-V block. This is due to an action on the refractory period of the A-V node. The ventricular muscle showed a decreased refractory period under the influence of therapeutic levels of the glycosides. Toxic levels of the glycosides further decreased the refractory period of the ventricle until the tissue was exposed to concentrations near those which initiate ventricular fibrillation.

It is likely that the glycosides affect the "margin of safety" of the A-V conduction tissue. There is probably a diminution in the stimulus for propagation, *i.e.*, the action potential. Furthermore, the threshold to stimuli in the tissue ahead of the oncoming impulse may be increased. Thus impulses would die out in the A-V conducting tissue and not reach the ventricles. In the toxic phase of A-V block elicited by the glycosides, Méndez and Méndez suggest that the speed of conduction is also markedly diminished.

Morrow *et al.* (1963) in their studies in dogs concluded that the major portion of the prolongation of the functional refractory period of the atrioventricular conduction system evoked by ouabain was dependent upon an intact autonomic innervation and myocardial catecholamine stores. Denervated hearts in animals, treated with reserpine to deplete catecholamine stores in the myocardium, showed a much smaller prolongation of the refractory period upon treatment with ouabain. In spite of this additional knowledge, the mechanism of the functional A-V block remains obscure.

Although digitoxin has been shown to bind to contractile protein and serum albumin, there is no convincing evidence to show that the molecules enter the cardiac cells. Stroud and Vander Veer (1937) hold the view that since the glycosides unite with cholesterol to form cholesterides, this combination reduced the conduction of the A-V node and bundle of His. It is likely that diminished conduction results from the binding of the glycosides with the conducting tissue constituents causing a shift in potassium and sodium ion balance in such a way as to suppress the electrical conduction of the tissue. A definitive explanation of this action remains for future studies to clarify.

*The third action of digitalis on the heart is the slowing of the cardiac rate.* This action has at least 2 components. The first of these is a direct effect upon the heart muscle itself. The second is through the stimulation of the vagal center, which is apparently mediated through the carotid sinus mechanism. In the same person with heart failure the vagal and extravagal actions will depend upon the dose of digitalis administered (Gold, 1940 *et seq.*). Small doses of digitalis produce cardiac slowing mainly by vagal action. This action of the drug is abolished by large doses of atropine. When the heart is digitalized and the optimal effect of the drug is produced, the extravagal slowing of the heart is as important a factor in the effect as the vagal action. The extravagal action is not abolished by atropine. Modell *et al.* (1941) showed that in patients with heart failure and atrial fibrillation under digitalis therapy, exercise would increase the pulse rate to 160 or 180 if the slowing was vagal only. If the slowing also was extravagal in character, exercise seldom accelerated the pulse above 100. The observation bespeaks the increase of digitalis dosage in individuals who suffer palpitation and dyspnea when they are active but are comfortable at rest.

Digitalis may achieve improvement in a patient without marked evidence of cardiac slowing. The slowing of the pulse rate by digitalis is most conspicuous in those patients who exhibit atrial fibrillation along with congestive failure. When the drug evokes cardiac compensation and restores normal vagal tone, the compensatory tachycardia of heart failure is abolished.

The vagal slowing of the heart produced by digitalis is likely mediated through the action of acetylcholine. Acetylcholine and digitalis produce cardiac slowing with a loss of potassium from the cardiac tissue. In addition, the work of Bülbring and Burn (1949) showed that the formation of acetylcholine in cardiac tissue is closely associated with the maintenance of cardiac rhythm. Those areas of the heart exhibiting the highest intrinsic rhythm (sinus) contain the greatest amount of acetylcholine (Mazel and Holland, 1958).

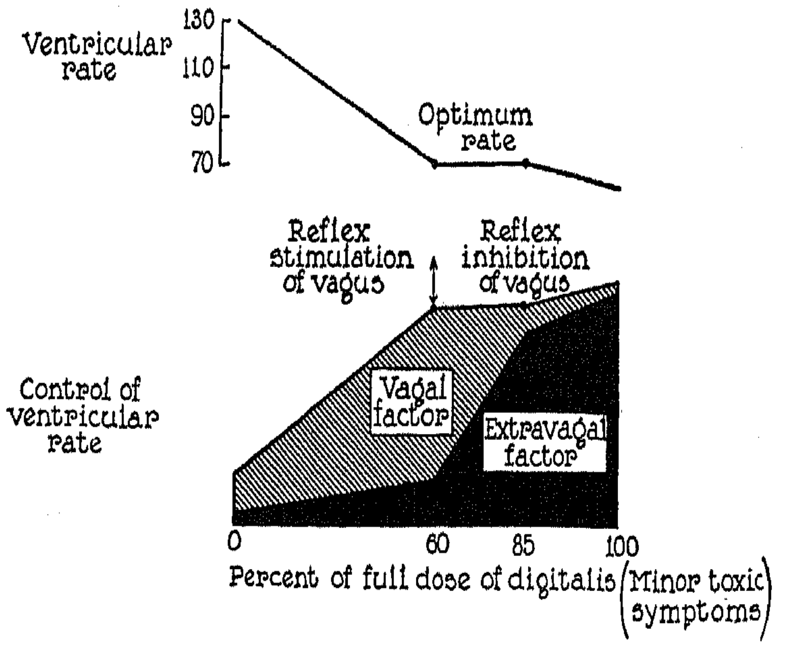


FIG. 40-2. Schematic representation of the mechanism by which digitalis slows the ventricular rate in heart failure with atrial fibrillation. (From H. Gold, N. T. Kwit, and M. Cattell: J. Pharmacol. & Exper. Therap., **69**: 177, 1940.)

In summary of the action of digitalis on the heart, the following statements may be gleaned from the foregoing discussion.

1. The most salutary effect of digitalis in congestive heart failure is that of increasing the contractile force of the heart enabling the tissue to convert available chemical energy into mechanical work. This is likely achieved by the mobilization of calcium ions in the myocardium and by alteration of the intracellular cationic ratio $Na^+/K^+$ and/or by direct action on the muscle protein.
2. Digitalis evokes a partial A-V block reducing the number of atrial impulses reaching the ventricular tissue in atrial fibrillation. The refractory period of the heart is prolonged.
3. Digitalis produces reflex vagal and extravagal cardiac slowing. The first response appears to be mediated through acetylcholine. The second is secondary to the restoration of compensation to the hypodynamic heart and is in sequence to the action of increasing the contractile force of the heart.

The vagal and extravagal effects of digitalis in cardiac slowing are shown schematically by Gold and his associates (1939), in figure 40-2.

**Electrocardiographic changes and digitalis.** It is obvious that the profound effect of digitalis on cardiac conduction should manifest itself in electrocardiographic changes. In the normal heart certain of the effects of the drug on the electrocardiogram are quite characteristic. In the diseased hearts these are frequently superimposed upon changes characteristic of the disease. The electrocardiogram frequently shows the summation of both effects. Only the changes produced in the normal heart will be discussed.

In a normal person the administration of digitalis in therapeutic doses causes, as a rule, a lowered T-wave amplitude. Repeated doses will obliterate and ultimately invert the T-wave.

The first electrocardiographic changes showing evidence of digitalization are usually a shortening of the Q-T interval, S-T segment scooping, and inversion of the first portion of the T-wave. If one injects a solution of digitoxin continuously into a laboratory animal such as a cat, which was formerly used in the assay of digitalis, other changes occur in rapid progression. These are:

1. Prolongation of the P-R interval
2. Atrial tachycardia
3. Ventricular tachycardia
4. Depression in S-T segment
5. Paroxysmal tachycardia with regular alternation in the direction of the ventricular complex
6. Ventricular fibrillation
7. Cardiac stoppage

The effect of digitoxin just prior to death is shown in figure 40-3. The animal used was a dog; the normal record is shown also.

**The effect of digitalis on blood pressure.** Digitalis produces no uniform effect upon the blood pressure. The response is individualistic and depends upon the state of the circulatory system prior to the administration of the drug. When administered in heart failure and a restoration is effected, there is generally an increase in systolic blood pressure and an increase in pulse pressure. The rise in systolic blood pressure is insignificant and does not interdict the use of the drug in hypertensive patients.

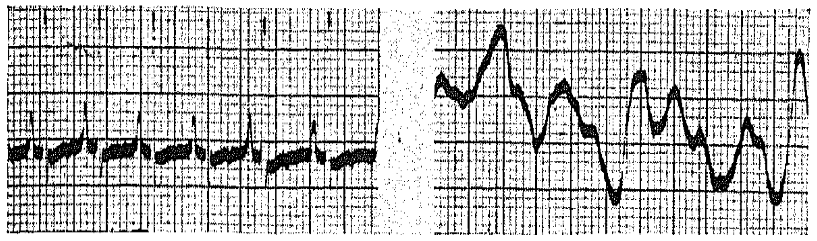


FIG. 40-3. Digitoxin on dog's heart (Lead II). (From F. K. Bell, C. J. Carr, and J. C. Krantz, Jr.: J. Pharmacol. & Exper. Therap., **89**: 143, 1947.)

Digitalis produces a slight constriction of the vessels in the splanchnic area and generally slight dilatation of the renal vessels. In congestive heart failure digitalis tends to establish an equilibrium between the cardiovascular system and the vasoconstrictor center. The resultant equilibration effects an improvement in the efficiency of the circulation.

**The effect of digitalis on venous pressure.** In congestive heart failure the venous pressure is increased. Venous stasis is produced as a result of cardiac inefficiency. The right atrium does not remain in complete diastole for a sufficiently long period to receive the blood supply from the venae cavae. This produces increased venous pressure. With the improved mechanical efficiency of the heart under digitalis therapy the chambers are emptied and filled more completely. A venous pressure of 20 cm. of water will fall to 10 or 5 cm. with the general improvement of cardiac efficiency. The increased venous return to the heart contributes to the increased cardiac output.

Katz *et al.* (1938) showed that digitalis caused an engorgement of the hepaticoportal system leading to a rise in portal pressure in the dog. Liver volume is also increased. Katz states, "It is my firm conviction that a large part of the action of digitalis is to increase the storage of blood in such reservoirs. Later, of course, as the heart improves, diuresis tends to complete the process of relieving congestion."

When the direct cardiac effect of digitalis is excluded, it has been demonstrated that the cardiac glycosides exert a marked effect directly upon the entire vascular system. In therapy in congestive heart failure, the direct cardiac effect masks the circulatory action. For example, Ross *et al.* (1960) demonstrated a generalized action of the digitalis glycosides on the circulation of dogs apart from the direct cardiotonic action. The cardiac action was excluded by means of a cardiopulmonary bypass. The glycosides acetylstrophanthin, ouabain, and lanotoside C when infused evoked a consistent augmentation of peripheral vascular resistance. When infused into the lower aorta, vascular resistance increased only in this portion of the vascular bed. The data indicate that increased peripheral resistance induced by the glycosides stems from a direct action on the arteriolar smooth muscle.

In subsequent experiments the effects of digitalis glycosides on the venous return were studied, again excluding the direct cardiac action. With intact portal circulation, the glycosides evoked a decline of venous return and intravascular pooling of blood occurred. When pooling in the splanchnic area was prevented, an increase in venous return was observed. Small increases in the superior and inferior vena caval pressures occurred. It appears, from these observations, that glycosides of digitalis induce a generalized venoconstriction that is most marked in the hepatic veins. It should be remembered that in these experiments the direct cardiac effects of the glycosides were excluded.

The effect on the venous return is compensatory and does not occur as a rule when the drug is administered to normal persons or in heart failure in which increased venous pressure is not a factor. The main action of the drug on venous return is effected when venous stasis occurs, and the action appears to be mediated mainly through an improved efficiency of the heart.

**The effect of digitalis on the coronary circulation.** There had been a clinical impression extant many years ago that digitalis preparations caused coronary artery constriction and often chest pain.

Gold and his associates (1938) studied the problem critically and reached the opposite view. Their evidence appears crucial. They selected 120 patients devoid of congestive heart failure but who suffered cardiac pain upon physical effort. These persons were given therapeutic doses of digitalis and placebos alternately. In 15 per cent of the patients receiving digitalis, cardiac pain was increased and in 30 per cent a diminished incidence of cardiac pain was recorded. The results were strikingly similar when a placebo was used instead of digitalis. Gold concludes, "In view of the fact that the patients of this series were presumably unusually susceptible to cardiac ischemia, the results indicate further that digitalis even in large doses rarely, if ever, produces effective constriction of the coronary arteries in man."

The matter therefore appears to be settled for the present that digitalis produces no demonstrable effect upon the coronary arteries in man *in situ*. Therefore, the drug is available in heart failure complicated with susceptibility to anginal pain.

**The effect of digitalis on the clotting of blood.** The consensus is that digitalis at therapeutic dosage levels does not affect the clotting time of blood.

**The effect of digitalis on the vomiting center.** It is well established that in many individuals digitalis produces nausea and vomiting. As this will occur upon the intravenous administration of digitoxin, the effect is not entirely due to gastrointestinal irritation. Gold *et al.* (1952) studied extensively the problem of the emetic action of digitalis in man. They observed that the gastrointestinal toxicity of the various cardiac glycosides exhibited a latent period of 10 hours in some cases. This latent period has been one of the reasons for the assumption that the effect was central and not local. By the administration of the glycosides intravenously or intramuscularly it was shown that a more pronounced cardiac effect could be achieved with much less gastrointestinal distress. Gold holds the view that these findings do not justify the use of parenteral instead of oral digitalis glycosides. However, it is possible in some cases that a more favorable cardiac response may be achieved with less emetic action by the parenteral use of the glycosides.

Digitalis stimulates reflexly the vagal center. The vomiting center lies adjacent to this brain center and is simultaneously stimulated by the action of the drug. Hatcher and Weiss (1922 and 1927) found that the direct application of the drug to the floor of the fourth ventricle did not elicit emesis. Borison and Wang (1953) in their comprehensive review of the physiology and pharmacology of vomiting, concluded that the digitalis glycosides evoke vomiting by acting at more than one receptor site. It is their opinion that the central site of emetic action is the medullary chemoreceptor trigger zone. Furthermore, the local irritating action on the gastrointestinal tract is likely to be insignificant under most circumstances.

**Diuretic effect of digitalis.** In recent years the direct diuretic action of the digitalis glycosides has been considered a definite possibility. This stems from studies in animals with experimental congestive heart failure in which increased aldosterone plasma levels have been demonstrated. This presumably is a partial cause of sodium retention in heart failure. It has been suggested that the glycosides possibly antagonize the effect of aldosterone at a tubular level similar to the spirolactones. Waldhausen and Herendeen (1963) studied the problem critically in dogs. These studies involved measurements of renal blood flow by cannulating a segment of the vena cava at the level of the renal veins. Therapeutic doses of acetylstrophanthin and ouabain caused a significant fall in renal blood flow in all of 26 animals. Renal vascular resistance rose 152 per cent while the peripheral vascular resistance rose only 65 per cent. They concluded that little or no diuretic effect of digitalis was due to direct renal action.

One must therefore, for the present, conclude that the diuretic effect of digitalis is a result of its improvement of heart action and the removal of circulatory embarrassment. It does not increase urine flow in therapeutic doses in normal individuals. The drug is not useful in the treatment of edema resulting from hydremic nephritis where there is no cardiac involvement.

**The effect of digitalis on striated muscle.** The specificity of digitalis for cardiac muscle arouses interest in the effect of the drug on striated muscle. The effect of digitoxin on the frog's sartorius muscle was investigated. The glycoside produced a gradual diminution of the twitch tension of the muscle. The effect was similar to an excess of potassium ions. A union of the glycoside with some cellular constituent of the striated muscle was postulated. This caused the cell to lose $K^+$, which resulted in an excess of $K^+$ in the fluid surrounding the cell.

Visscher (1938) showed that the tissue of the heart-lung preparation of the dog also showed a potassium loss under the influence of the cardiac glycosides. Cattell (1942) injected ouabain intravenously into dogs within therapeutic limits. He measured the urinary potassium excretion prior to and after ouabain; the potassium excretion was uniformly high during the first few hours after the administration of the glycoside. There was also a rise in potassium blood levels in the dogs.

The loss of potassium by the myocardium as a facet of the action of digitalis is undergoing close scrutiny. Tuttle *et al.* (1962) using rabbits' atria contend that potassium loss is only achieved at levels of the glycosides that are not used in therapeutics. It does appear, however, from the available evidence that there is an outflux of potassium from the myocardium sequential to digitalis action. Perhaps the divergent results of various investigators stem from species variation and difference in experimental design.

One of the properties which appears to be distinctive for the potassium ion is its high rate of diffusion through cell membranes. That its release from the myocardium is associated with the beneficial effect of digitalis is not surprising, since the migration of the potassium ion links the electrical phenomenon of excitation with the biochemical process of energy release for contraction.

The important practical interest of this observation in our opinion lies in the difference between the response of the 2 types of muscle to the drug. Ouabain, page 643, increased the tension of papillary muscle. Digitoxin diminished the twitch tension of striated muscle.

**Digitalis and the calcium ion.** For many years the view has been held that $Ca^{++}$ synergizes the action of digitalis on the heart. Nyriri and DuBois (1930) showed that an increase of 3- to 4-fold in the $Ca^{++}$ concentration in the perfusion fluid "reinforces" the effect of digitalis on the myocardium and initiates a more prompt action. It does not appear that digitalis evokes a mobilization of cellular calcium in the myocardium. The importance of the calcium ion in the maintenance of normal muscle contractility establishes its blood level as a matter of paramount importance in the therapeutic action and toxicity of digitalis.

Gold and Edwards (1927) found that in dogs with hypercalcemia induced by injections of parathyroid hormone, a greater susceptibility to ouabain was produced. Bower and Mengle (1936) reported 2 deaths resulting from the intravenous injection of calcium gluconate in digitalized patients. In our present state of knowledge one must accept the injection of calcium salt solutions into digitalized patients as a potentially dangerous procedure.

**Absorption, distribution, and excretion of digitalis.** Digitalis and its preparations are absorbed from the gastrointestinal tract. There is no convincing evidence to show that the glycosides are deleteriously affected by the juices of the alimentary tract. The glycosides which are lipoid-soluble, such as digoxin, digitoxin, acetyldigitoxin, and gitalin, are readily absorbed upon oral administration. Those which are water-soluble, such as ouabain are, very poorly absorbed. There is evidence that digitoxin is bound in the blood by serum protein. Spratt and Okita (1958) observed that 1 mg. of rat serum protein will bind 0.01 μg. of digitoxin when administered within the therapeutic dosage range.

The absorption, distribution, and excretion of the digitalis glycosides have been studied by Friedman *et al.* (1952), using the embryonic heart of the duck, which is very sensitive to digitalis glycosides, as a test for urinary excretion. Studies were conducted also by Okita *et al.* (1953) using $C^{14}$-labeled digitoxin. More recent studies by Doherty and Perkins (1962) were performed using "tritiated" digoxin.

For the most part, the results of the independent studies are in agreement; the following statements represent a general consensus. Normal and cardiac patients excrete the drug in approximately the same manner. With toxic manifestations, larger quantities are excreted. The liver is the principal organ of detoxification and will detoxify about 50 μg. of digitoxin daily. The heart exhibits no special avidity for the glycosides. The kidney is the major organ of excretion of the glycosides and their metabolic products; about 12 per cent is excreted in the feces (Okita *et al.*, 1955).

With the intravenous injection of "tritiated" digoxin the following average excretion schedule was observed: 24 hours, 38 per cent; 7 days, 80 per cent, with 11.7 per cent in the stools at 7 days.

The fate in the body of the digitalis glycosides is not completely understood. The glycosides accumulate and then undergo a rather uniform rate of degradation for long periods of time. This is of great clinical advantage. Once the heart is digitalized by repeated dosage, owing to the cumulative effect a so-called maintenance dose may then be given. For the average patient this is 100 to 200 mg. of the powdered leaf or 0.1 to 0.2 mg. of digitoxin. This represents the daily amount which is destroyed and excreted.

**The toxic manifestations of digitalis.** William Withering keenly observed the toxic manifestations of digitalis. There are numerous cases of digitalis poisoning because of neglect of the recognition of the danger signals. The full therapeutic effect of digitalis in most cases is experienced only with doses that produce some minor toxic symptoms. These are most frequently *nausea* and *vomiting*. When these symptoms persist, the dosage should be reduced. The fundamental requirement in avoiding intoxication with digitalis is to administer the *minimal effective dose*.

The signs and symptoms of digitalis intoxication do not occur in regular sequence. Headache and nervous irritability may precede or go along with gastrointestinal distress. Greenish yellow vision and flickering sensations are common. Visual symptoms are a frequent and almost always faithful symptom of intoxication in a patient receiving digitalis. *Abdominal pains, paresthesias, tingling of the extremities*, and *facial neuralgia*, have also been encountered.

The cardiac manifestations that may occur are extraventricular systoles resulting from a hyperirritability of the heart. These may pass into ventricular fibrillation and death. The intravenous use of the pure glycosides must be regarded with great caution owing to the incidence of toxic manifestations. When intoxication does occur it is clear that the drug must be discontinued for a period. Intoxication with digitalis may occur if the patient is taking one of the thiazide diuretics that have a tendency to produce hypokalemia. In these cases potassium chloride, 2 to 3 gm. daily orally, has been beneficial. Excessive quantities of potassium salts should be avoided in patients with uremia.

In digitalis intoxication, the inhibition of A-V conduction is secondary to a direct effect of the drug upon the A-V junctional tissue, mediated primarily through vagal action. In this condition potassium acts directly on the A-V node to enhance the block. Therefore, if the A-V block is secondary to the primary action of digitalis, potassium salts should be administered cautiously with frequent observations to determine whether or not the A-V block is being aggravated (Fisch *et al.*, 1963).

It was stated previously that calcium ions synergize the cardiac action of digitalis. Several investigators have used the calcium ion chelating agent sodium versenate (page 948) to combat digitalis intoxication. Bechtel *et al.* (1956) showed that 3 gm. of sodium versenate may be given intravenously during a period of 30 minutes with only minor side effects such as tingling of the lips. Gubner and Kallman (1957) reported success in the reversal of digitalis intoxication using 600 mg. of the chelating agent. Supraventricular and ventricular arrhythmias and ectopic beats not caused by digitalis were abolished by the chelating antidote. Jick and Karsh (1959) used sodium versenate in 27 patients with cardiac arrhythmias or conduction disturbances. In cases in which the cardiac disturbance was not due to digitalis, sodium versenate was not beneficial. In those in which digitalis was the incriminating factor, there was a prompt reversal of the toxic action of digitalis. In some cases the reversal was temporary, in others permanent. Thus, this agent lends itself as a means to differentiate between digitalis-induced disturbances of cardiac rhythm and those which are unrelated to the drug. Since the administration of potassium salts is not without hazard in digitalis intoxication, the use of sodium versenate would appear to offer advantage in promptness of action and relative freedom from adverse side effects.

**The standardization of digitalis preparations.** *Digitalis purpurea*, grown under various conditions and in different localities, varies greatly in its cardiotonic activity. This inherent variation may be as much as from 50 to 200 per cent among different samples. Prior to the biologic method of standardizing the leaf and its preparations on the frog, tremendous variations were extant among the clinically used products. Some were virtually useless and others were toxic if used in therapeutic dosage levels.

The frog and cat have been the principal animals upon which digitalis preparations were standardized in former years. Extensive bioassays with the pigeon instead of the cat as a test subject revealed that a reproducibility equal to that with the cat assay could be achieved with pigeons. The pigeon is more readily available and is now the official test subject for the assay of digitalis. The method is an intravenous lethality measurement under standardized conditions. The potency of the digitalis tested is compared with that of the U.S.P. *Digitalis Reference Powder. The U.S.P. digitalis unit is the potency equivalent to 0.1 gm. of U.S.P. Digitalis Reference Powder.* The United States Pharmacopeia requires not less than 0.85

U.S.P. digitalis unit per 0.1 gm. of digitalis powder.

The use of U.S.P. digitoxin obviates much of the danger of wide variation in cardiotonic activity. The official product contains 90 to 100 per cent in the pure glycoside. Chemical tests assure the certainty of at least this degree of reproducibility. There appears to be no advantage in the administration of digitalis leaf that cannot be achieved with the use of digitoxin or one of its glycosides.

Bell and Krantz (1945) developed a chemical assay for digitalis. The method depends upon the formation of an orange color by interaction between the unsaturated lactone portion of the genin molecule with an alkaline picrate solution. The method usually agrees well with biologic assays, especially for tablets of digitoxin. This chemical procedure is recognized by the U. S. Pharmacopeia to assure the potency of digitoxin and its preparations.

The digitalis preparations in the United States are now adequately standardized. The use of the chemically pure glycosides will undoubtedly make biologic methods unnecessary.

### The therapeutic uses of digitalis.

1. Digitalis is indicated in *congestive heart failure* with or without *atrial fibrillation*. In these conditions digitalis is strikingly useful. When given in other conditions it is generally of no value or might be distinctly harmful. Indeed, when administered to normal subjects at rest or during exercise, digoxin and acetylstrophanthin evoked a decrease in cardiac output.

2. In atrial fibrillation the drug has little effect upon the fibrillating atria. Fibrillation continues, but the partial block of the conduction enables the ventricles to establish their independent, slowed, effective beat. The drug does not cure the condition and must be continued, as a rule, throughout life. Digitalis, however, enables the patient to assume a moderate degree of activity. It mitigates the dyspnea. The circulatory improvement relieves the anasarca and ascites and permits a more comfortable life.

The effect of deslanoside on a patient with congestive heart failure and atrial fibrillation is shown in figure 40-4 by DeGraff (1958). Note the rapidity of digitalization upon the intravenous administration of the glycoside.

**The choice of a digitalis preparation.** In the choice of a satisfactory digitalis preparation DeGraff (1946) states there are 3 important considerations:

1. The latent period before action
2. The rate of dissipation
3. The rate and completeness of absorption

The dosage schedule for each digitalis glycoside is specific and varies from patient to patient. There is no fixed single dose or maintenance for all patients. Average dosage schedules indicate only the area of dosage for the individual digitalis glycosides.

For a first approximation of the dosage of the glycosides the following data are set forth in table 40-3.

For routine digitalization of patients who are not seriously decompensated, digitoxin, digoxin, or digitalis leaf given orally appear to be most generally used. With digitoxin the period of maximal effect is 2 to 9 hours and the duration is about 21 days. With digitalis leaf the maximal effect is slower (12 to 48 hours) and the duration is about 17 days. On the other hand, the onset of action of digoxin is shorter (4 to 6 hours) and its period of dissipation (4 to 7 days). The rapid period of dissipation of digoxin is advantageous. This is especially true when toxic manifestations occur. For this reason it appears that digoxin is gaining favor among many cardiologists.

For an acutely decompensated patient the latent period which precedes the activity of digitalis leaf, digitoxin, or digoxin is objectionable and may be fatal. Digitalization of such patients using the rapidly acting glycoside deslanoside intravenously achieves the full effect in 60 to 90 minutes, as shown in figure 40-4. Ouabain (strophanthin G) may also be used; 0.6 mg. is given intravenously, the effect is achieved in 10 to 30 minutes, and subsequent doses of 0.1 mg. may be given in ½ hour intervals until a total of 1 mg. has been given. After digitalization occurs, one of the orally active glycosides may be used for maintenance, since ouabain is not well absorbed from the gastrointestinal tract. Where time is of the essence in the digitalization of the patient, intravenous medication with deslanoside, ouabain, or strophanthin K is indicated.

For children with heart failure digoxin, because of its rapid period of dissipation, seems to be the glycoside of choice (Sapin *et al.*, 1959). For infants and children up to 10 years, digitalization is achieved with 0.01 mg./pound of body weight repeated every 6 hours as required. Maintenance therapy usually requires 0.01 mg./pound of body

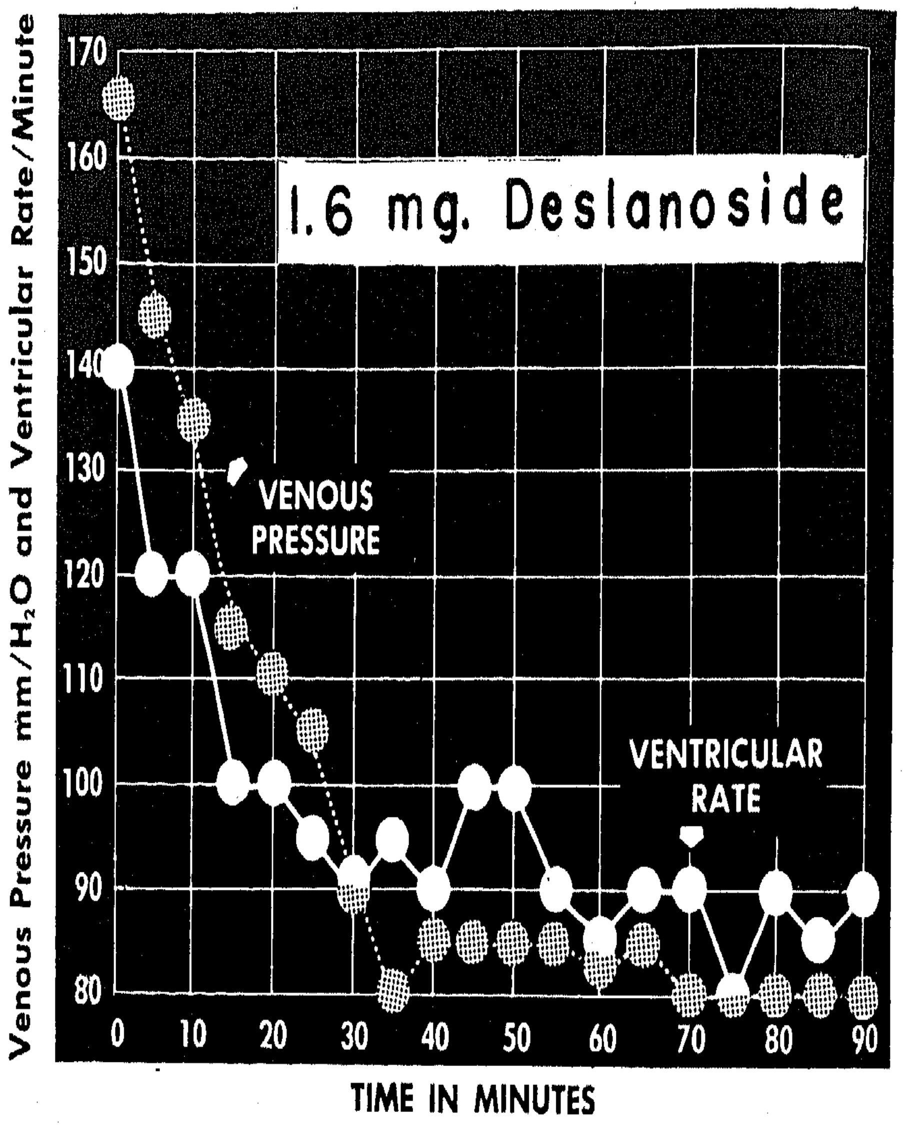


FIG. 40-4. The effect of cedilanid-d (Deslanoside, U.S.P.) administered intravenously to a patient with congestive heart failure and atrial fibrillation. (From A. C. De Graff, personal communication, 1958.)

weight once daily or in divided doses. The glycoside is available in a pediatric elixir, 0.05 mg./ml.

**Amorphous gitalin** is gaining a degree of prominence as a cardiac glycoside. Like digoxin, it has a short period of dissipation. Batterman *et al.* (1952) found gitalin to exhibit a margin of safety greater than digitalis leaf, digitoxin, or digoxin. They found absorption dependable in their series of patients. On the average, for therapeutic effect 100 mg. of digitalis leaf was equivalent to 0.46 mg. of gitalin. On the other hand, for toxic manifestations 100 mg. of digitalis was equivalent to 0.65 mg. of gitalin. However, Gruhzit and Farah (1953) observed that gitalin did not exhibit a greater margin of safety (between the therapeutic and the toxic doses) than did the other cardiac glycosides. Their studies were conducted on the failing heart of the dog in heart-lung preparations.

The daily maintenance dose of amorphous gitalin is 0.5 mg. Toxic effects appear to be uncommon. When these occur they are similar to those evoked by digitoxin. Weiss and Steigmann (1954) used double the maintenance dose in a series of patients; toxicity symptoms occurred in 22 per cent of the cases. Certain patients were able to tolerate from 3 to 6 times the daily maintenance dose without serious side effects. This bespeaks the wider clinical margin of safety of amorphous gitalin.

Amorphous gitalin is also available for the rapid intravenous digitalization of patients in whom the oral route is not feasible, especially those with acute, congestive cardiac decompensation. The initial dose intravenously is 2.5 mg. twice in 24 hours. The total digitalizing dose is 5 to 6 mg.

**Acylcanid.** This derivative of digitoxin is *acetyl-digitoxin alpha*. Acylcanid is obtained from lanotoside A by enzymic cleavage. Its pharmacologic action lies intermediate between that of digitoxin and that of digoxin. Zilli and Luisada (1955) found Acylcanid to elicit toxic effects similar to those of digitoxin; however, they appeared to be less severe and of shorter duration. The persistence in the body is of shorter duration than that of digitoxin. Maher and Pullen (1955) found that the digitalization dose of Acylcanid varied from 1.5 to 3 mg. The drug is administered in divided doses over a 48-hour period. The usual daily maintenance dose is 0.1 to 0.4 mg. daily.

TABLE 40-3

*Dosage of Cardiac Glycosides (DeGraff, 1958)*

| Oral | Average Digitalizing Dose | Daily Maintenance Dose |
|---|---|---|
| | *mg.* | |
| Acetyl Digitoxin | 2.4 in 24 hours to 4.0 in 4 days | 0.1 to 0.4 |
| Digitoxin | 2.2 | 0.15 |
| Digoxin | 3.75 | 0.5 |
| Lanatoside C | 7.0 in 24 hours<br>16.0 in 72 hours | 0.5 to 1.0 |
| Gitalin | 6.0 | 0.5 |

| Parenteral | Average Safe Intravenous Dose in 2 Hours | Daily Maintenance Dose |
|---|---|---|
| Ouabain | 1.0 | Cannot be given as a maintenance dose orally |
| K-strophanthin | 1.0 | |
| Desacetyl lanatoside C (Cedilanid-D) | 1.0 | |

There are many cardiac glycosides available in a variety of dosage forms. With all of these drugs the margin of safety is narrow and the dosage schedule must be individualized to meet the patient's needs. Correct digitalis therapy is an art; it takes much experience to master it. The administration of the drug is a type of biologic titration, striving for "the endpoint" of adequate restoration of compensation with a minimum of side effects. Scherf (1958) very cogently commented, "It does not matter much which type of digitalis preparation is used but how it is used."

**Other plants with cardiotonic glycosides.** Foremost among the digitalis allies is *Strophanthus gratus*, which contains the cardiotonic glycoside ouabain (strophanthin G). The glycoside is recognized by the U. S. Pharmacopeia. Its use in the treatment of cardiac failure as an emergency drug is given on page 651.

Squill, *Urginea maritima*, contains *Scillaren*, a cardiotonic glycoside. The squill glycosides are available under the name of *Urginin.* Urginin is composed of crystalline and amorphous *scillonins* combined. It is an effective cardiotonic drug. Its action is similar to digitalis. It appears to offer no advantage over digitalis. Urginin has been used successfully in patients who cannot tolerate digitalis well. This condition is not frequently encountered.

*Convallaria majalis* (lily of the valley) contains the glycoside *Convallotoxin*. It has been used as a digitalis substitute. There seems to be no advantage offered by the drug or its glycoside. *Apocynum cannabinum* (Canadian hemp) contains the glycoside *Cymarin* which exhibits cardiotonic activity. It is not generally used.

Certain toad poisons exhibit digitalis activity. A typical example of these is *Bufotoxin* from *Bufo vulgaris.* The aglycone of bufotoxin known as *Bufotalin* resembles the aglycone of scillaren A. Chen and Chen (1933) studied the compound pharmacologically and found its action in general similar to digitalis.

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# 41

# *The Response of the Myocardium to the Antifibrillatory Drugs*

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There are several drugs which owe their therapeutic value to their capacity to depress the myocardium. They are employed in arresting disturbances in cardiac rhythm, hence they are often referred to as *antiarrhythmic drugs*. The term antifibrillatory drug is used for those agents capable of restoring sinus rhythm in cases of atrial or ventricular fibrillation and in severe tachycardias. They also are used in heart block and conduction abnormalities. The principal drugs in this category are *quinidine*, *procainamide* and certain *sympathomimetic amines.*

## QUINIDINE

**Quinidine Sulfate, U.S.P.** Quinidine is the sulfate of an alkaloid obtained from cinchona bark. It is the *d*-stereoisomer of the alkaloid quinine, page 157. It occurs as a white crystalline powder, often cohering in masses. The salt is soluble in water to the extent of about 1 per cent. Like quinine it evokes a very bitter taste.

The use of quinidine in the treatment of cardiac arrhythmias began with the observation of Wenckebach (1914). A Dutch merchant who was one of the patients of the Viennese physician called for treatment of atrial fibrillation attacks which disturbed him frequently. The merchant related that when the attack occurred he could check it himself by the taking of quinine which he took while in the malarious low countries. He demonstrated the value of quinine to Wenckebach. So impressed was the physician by the value of quinine in checking the paroxysmal type of atrial fibrillation in the merchant that he studied the problem further and found quinine a useful drug. In 1918 Frey used quinidine instead of quinine in atrial fibrillation. He found quinidine to be superior.

**Quinidine and quinine.** In the discussion of the use of quinine in the treatment of malaria, page 159, it was stated that quinine is a protoplasmic poison. Quinidine shares this action with quinine but is somewhat milder. Quinidine is less valuable in the treatment of malaria. The depressant action of quinine on the contraction of skeletal muscle was mentioned previously. Quinine is a depressant to skeletal muscle and antagonizes the muscle contraction produced by acetylcholine or neostigmine. Quinidine shares this action with quinine. On the myocardium the depressant action of quinidine is greater than that of quinine.

**Pharmacologic responses to quinidine.** The principal action of quinidine is on the heart. The alkaloid increases the refractoriness of various cardiac structures. Its value in disordered cardiac rhythm is dependent upon this action. The cardiac and extracardiac actions of quinidine have many components. These are set forth under the following headings:

1. *Quinidine increases the refractory period of the myocardium.* This has been demonstrated by the application of electrical stimuli at varying intervals between the beats of a rhythmically-beating heart. Stimuli applied far enough from the previous beat will elicit a response. Those applied too near the previous beat evoke no response. The longest time interval between the normal beat and the extra stimulus which fails to bring forth a response is one of the ways of measuring the refractory period. Quinidine is capable of increasing by 100 per cent the time interval between the previous beat and the period when the myocardium is susceptible to another stimulus.

It is generally considered that quinidine prolongs the "effective" refractory period without prolonging the absolute period. This involves cardiac "latency." The *latent period is the interval elapsing between the application of the stimulus and the response to the stimulus.* This is increased by quinidine thus providing protection from the effective action of rapidly repeated stimuli. Latency is drastically reduced during hypothermia, and quinidine provides protection of the heart from arrhythmias during this period of cardiac vulnerability.

2. *Quinidine diminishes the speed of electrical conduction in the myocardium.* This may be determined by the application of electrical stimuli to the myocardium and the measurement of conduction between 2 points in the normal heart and in the heart after quinidine.

The effect of quinidine on the electrocardiogram of the normal dog is shown in figure 41-1.

3. *Quinidine* suppresses *fibrillation of the myocardium.* Atrial fibrillation can be terminated by quinidine in animals and man. Ventricular fibrillation can be frequently prevented by quinidine. Wégria and Nickerson (1943) established that quinidine raised significantly and for a considerable period of time the fibrillation threshold of the dog's heart. When, however, the drug was administered very rapidly or in toxic doses, quinidine evoked ventricular fibrillation similar to toxic doses of digitoxin.

4. *Quinidine depresses directly the cardiac rhythmic function.* The sinus rhythm may be slowed by quinidine. Its action is not opposed by atropine, indicating that it is not mediated through the cardiac vagus. Ectopic pacemakers are slowed by quinidine, and in sufficient dosage the alkaloid is capable of suppressing the rhythmic activity of the entire heart.

5. *Quinidine retards the electrical systole of the heart.* In the electrocardiogram this is observed by a prolongation of the QRS duration and the Q-T interval.

6. *Quinidine in large doses may reduce the contractile force of the heart.* This may be demonstrated by the action of the drug on isolated strips of cardiac muscle. This action does not appear to be a serious hazard in therapy, as sufficient levels to elicit this response are seldom used in the treatment of disorders of cardiac rhythm with the drug.

7. *Quinidine blocks the vagus nerve in the heart.* The action is similar to atropine and hence opposes the cardiac slowing produced by acetylcholine.

Quinidine permits the sinus node to accelerate and may produce a tachycardia. To a lesser degree the drug facilitates A-V conduction by obliterating the vagal damper and thus may lead to an increased ventricular rate. For example, in atrial flutter a 2 to 1 block may be increased to a 1:1 ratio by a greater number of the atrial impulses reaching the ventricles.

If this vagal action is not obliterated by the other effects of the drug on the heart, the heart rate may be accelerated by quinidine. The acceleration of the cardiac rate is related to the phase of quinidine administration. After intravenous quinidine administration, the heart rate increases significantly in the initial stage; however, after moderate amounts of quinidine

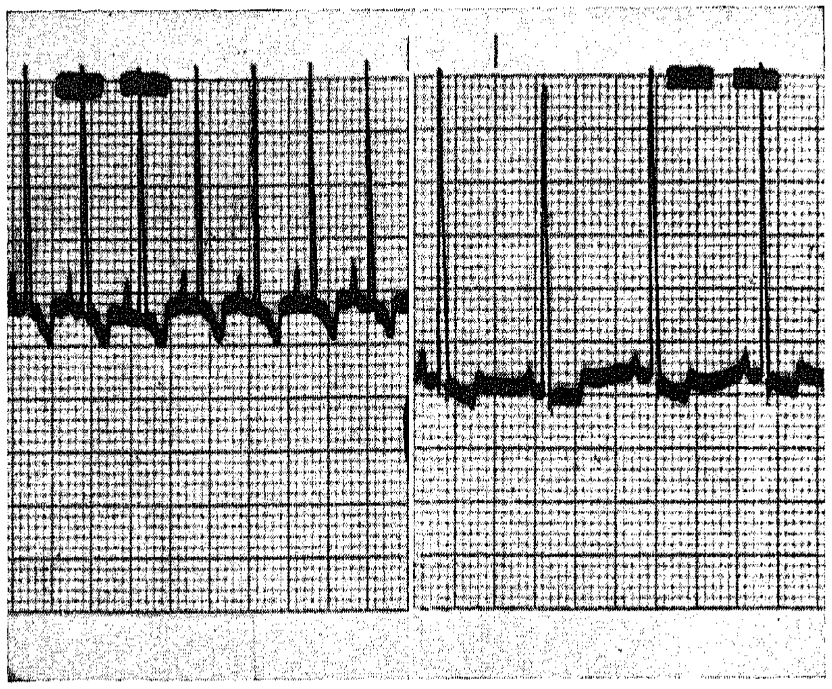

FIG. 41-1. Quinidine on the heart of the dog. *Left*, normal; *right*, after 60 mg./kg. of quinidine sulfate.

injection, the heart rate will slow. This is apparently due to the direct action on the S-A node. This action of the drug is opposite to that of digitalis, which reflexly stimulates the vagus.

8. *Quinidine in large doses produces a vasodepressor response.* This seldom occurs after oral therapeutic doses. Rapid intravenous doses of the drug generally elicit a depressor response. Lu (1951) demonstrated the direct vascular dilating effect of quinidine by intra-arterial injections in a denervated dog leg. An increase in leg volume was produced. The absence of central depression of the vasomotor center was demonstrated by intracisternal injections of quinidine sulfate. No blood pressure or leg volume changes ensued.

**Mechanism of action of quinidine.** Quinidine has been shown to depress the oxygen uptake and inhibit anaerobic glycolysis in slices of rat's atrial tissue. Thus it appears likely that this depression of metabolic activity in cardiac tissue is one of the facets of the action of quinidine. It has been suggested that quinidine interferes with the normal functioning in cardiac tissue of those processes which require acetylcholine. Briscoe and Burn (1954) demonstrated that quinidine added to a bath in which the isolated atria of the rabbit's heart were actively beating diminished the rate and amplitude of contractions. Ultimately the tissue was brought to a standstill. Acetylcholine added to the bath reestablished the atrial activity.

Armitage (1957) suggests that the depression of the rate and amplitude of contraction of the perfused isolated rabbit's heart evoked by quinidine is due to a diminution of the permeability of the cellular membranes of the organ to potassium ions. The action of quinidine was reversed by lowering the concentration of $K^+$ in the perfusion fluid. Furthermore, during the period of depression of cardiac activity elicited by quinidine, the usual inhibitory action of acetylcholine was reversed to one of stimulation. The stimulating action of acetylcholine is likely to be due to its capacity to increase the permeability of the cardiac cells to the $K^+$. Thus, it appears possible that the depressant action of quinidine on the heart may be mediated through its action in diminishing the outward flux of $K^+$. Holland (1957) suggests that the action of quinidine is mediated through the blocking of the release of acetylcholine from its intracellular sites. Since the stimulating action of acetylcholine is probably due to increasing the outward flux of $K^+$, the blocking of acetylcholine by quinidine correlates well with the action of the latter agent, causing a lowered permeability of the cardiac cell to the $K^+$ outward flux. It is of interest to note again that the myocardial increase in contractility produced by digitalis is likely associated with an increase of the outward flux of $K^+$.

**Fate of quinidine in the body.** Quinidine is absorbed readily from the gastrointestinal tract. The compound is partially removed from the circulation by the liver. Like quinine it leaves the

blood rapidly and is destroyed by the tissues. About 20 per cent of the compound is excreted unchanged in the urine.

Blood levels of quinidine after oral administration have confirmed the efficient absorption of the drug from the alimentary tract. Sokolow and Edgar (1950) observed that 28 of 30 patients converted from atrial fibrillation or flutter to sinus rhythm with a dosage of 400 to 600 mg. every 2 hours for 5 doses. Peak plasma concentrations occurred in 2 to 3 hours. The average conversion level was about 6 mg./L.; most of the patients converted at levels between 4 and 9 mg./L. Sokolow and Perloff (1961) observed that toxic manifestations at less than 6 mg./L. were seldom and never occurred below 3 mg./L. Myocardial toxicity occurred in 65 per cent of the patients at levels of 14 mg./L. Thus, it is clear that the efficacy of the alkaloid in converting atrial fibrillation to normal sinus rhythm parallels for the most part the curve of plasma concentrations.

**Toxic side effects and tolerance with quinidine.** Quinidine, like quinine, is prone to produce a group of symptoms known as *cinchonism.* These are *tinnitus aurium*, *blurring of vision*, *vertigo*, *tremor*, and *light-headedness. Gastrointestinal distress* is not uncommon. The gastrointestinal symptoms are likely to be local in character, as they occur after oral doses before the bulk of the drug is absorbed. In certain idiosyncratic individuals, quinidine may produce *urticaria*, *purpura*, or *asthma.* One absolute contraindication to therapy with quinidine is a previous history of *thrombocytopenic purpura* upon the administration of the drug. Fortunately, this untoward response is rare. It has been shown that the administration of quinidine diminishes the coagulation time of blood and decreases the number of thrombocytes without influence on the prothrombin or clotting time.

The side effects of quinidine vary from patient to patient. Some patients tolerate 2 gm. or more a day without symptoms. Others experience distressing symptoms with 0.3 gm. daily. When the dose is established to correct the disordered rhythm, it appears that neither tolerance nor susceptibility is acquired.

**The therapeutic uses of quinidine.**

1. Quinidine is useful in the treatment of *atrial fibrillation.* Quinidine, unlike digitalis, acts directly upon the fibrillating atria and may terminate the fibrillation, restoring the atria to normal rhythm. The drug appears to be most successful in cases of recent origin. Quinidine has been referred to as a "broad-spectrum" agent for the treatment of cardiac arrhythmias. In addition to its use in atrial fibrillation and flutter it is valuable for the purpose of preventing or terminating *atrial extrasystoles*, *paroxysmal supraventricular tachycardia*, *paroxysmal ventricular tachycardia*, and *ventricular extrasystoles.*

Quinidine decreases the number of discharges from the S-A node. The refractory period may be increased from 50 to 100 per cent. This permits a retreat of the wave of excitation before the muscle becomes capable of response. The atrial rate is slowed. The diminution of conduction reduces the number of impulses which pass over the conducting bundle. Atrial and ventricular filling is more complete, and the efficiency of the heart is improved.

Quinidine sulfate tablets or capsules 0.2 gm. are generally given every 2 hours cautiously over a period of a day. If the patient tolerates the drug well the dose may be increased to 0.4 gm., generally not exceeding 2 gm. in the course of a day. The maintenance dose in successful cases is from 0.2 to 0.4 gm. 3 to 4 times daily. Quinidine is discontinued if the QRS duration increases or other signs of toxicity become manifest. In impairment of renal function quinidine intoxication may occur owing to the diminution of the excretion rate of the drug.

Solution of Quinidine Gluconate, N.F., 80 mg. /ml. is available for intramuscular use when the oral route is unavailable. The action is more prompt parenterally than orally. Quinidine gluconate injection may be given intravenously in emergency cases. The injection must be made slowly and frequent blood pressures recorded. If severe hypotension occurs, it may be combated by the administration of a suitable sympathomimetic amine. Following rapid intravenous administration of quinidine, Scherlis *et al.* (1961) demonstrated that the quinidine level in the coronary sinus transiently exceeded that in arterial blood. The myocardial concentration of quinidine exceeded the concentration in the blood from 4- to 10-fold.

For patients who do not tolerate quinidine sulfate well because of gastrointestinal distress, quinidine polygalacturonate (Cardioquin) is indicated. Polygalacturonic acid serves as a buffering moiety, protecting the mucosa of the stomach. It permits dependable absorption of the quinidine. The product contains 60.46 per cent of quinidine and is available in tablets containing 275 mg. of quinidine polygalacturonate, equivalent to 200 mg. of quinidine sulfate.

In susceptible individuals quinidine may give rise to *cinchonism*, as does quinine frequently. There is a slight possibility of the drug dislodging a clot in an atrial appendage in an old case of fibrillation by reinstituting effective atrial beats. In addition, in some individuals quinidine may cause the atrial fibrillation to pass to ventricular fibrillation owing to insufficient blocking of A-V conduction. For this reason quinidine is frequently given to the digitalized patient. The initial digitalis therapy more completely effects the A-V block and diminishes the possibility of tachycardia. The onset of ventricular premature contractions or ventricular tachycardia upon quinidine therapy enjoins immediate cessation of the use of the drug.

The combined use of digitalis and quinidine has proved successful in the hands of many cardiologists. Weisman (1959) is of the opinion that previous digitalization offers advantages in most cases of atrial fibrillation in which quinidine is to be administered. Owing to diminished efficiency and metabolic disturbances in the fibrillating heart, he feels that the use of digitalis to improve the physiologic state of the heart is desirable. Furthermore, lower dosage levels of quinidine are required; the chances of success are enhanced.

Although quinidine is safer and more successful in cases of atrial fibrillation of recent origin, a longer duration of the arrhythmia does not preclude success with quinidine therapy. Success in various series of cases reported vary from 53 to 89 per cent. An enlarged heart with congestive failure often bespeaks failure of quinidine therapy.

The recent advent of countershock of electrical conversion of arrhythmias has made a revolutionary change in the treatment of cardiac arrhythmias. This new method is safe, simple, and quite effective. Thus, the role of quinidine for the conversion of arrhythmias has decreased considerably. Nevertheless, quinidine remains as an important antiarrhythmic drug, as it is useful for the prevention of recurrent arrhythmias and also in facilitating the electrical method of conversion.

### Procainamide Hydrochloride, U.S.P.

**Procainamide Hydrochloride, U.S.P. (Pronestyl Hydrochloride).** Procainamide is used in the treatment of ventricular arrhythmias. Owing to its relation to procaine, the drug was mentioned on page 635. Procainamide differs chemically from procaine only by the presence of the amide grouping (·CO·NH) in the molecule where procaine has the ester grouping (·CO·O·).

Procainamide hydrochloride occurs as a white, crystalline powder which is freely soluble in water.

**Pharmacologic action and therapeutic use of Procainamide.** Procainamide, unlike procaine, is not readily hydrolyzed by plasma. For example, procaine is 100 per cent hydrolyzed in 6 minutes, whereas procainamide is only 7.5 per cent hydrolyzed in 19 hours. As a local anesthetic, procainamide is as potent as procaine; the local anesthesia with the amide is somewhat more sustained. Like procaine, procainamide will block the cardiac arrhythmias produced by a challenging dose of epinephrine in animals under cyclopropane anesthesia. The action of procainamide on the myocardium in reducing excitability and conduction is the principal response elicited by the compound.

Mark *et al.* (1951) studied the action of procainamide in blocking ventricular arrhythmias in the dog. These were induced by epinephrine in the animal under cyclopropane anesthesia. These investigators found the amide more effective than quinidine and also less toxic in the treatment of ventricular arrhythmias in man. The drug is established in the treatment of ventricular arrhythmias. It is available by intravenous and oral administration.

McClendon *et al.* (1951) studied the circulatory changes which occur in patients upon the intravenous administration of procainamide. They were as follows: usually a reduction in cardiac output, diminished blood flow through the pulmonary vessels, fall in pulmonary arterial pressure, a fall in mean radial arterial pressure, variable changes in peripheral resistance, and a significant slowing of velocity of blood flow. They were of the opinion that these changes are mediated mainly through the depressant action of procainamide on the heart.

The question of specificity of the action of procaine on the ventricles has been given special study. Kayden *et al.* (1951) confirmed the findings of others in demonstrating the effectiveness of procainamide in ventricular arrhythmias. They further showed that in 24 cases of chronic atrial flutter and fibrillation the drug was not effective in reestablishing normal rhythm. However, in 2 recent cases of atrial fibrillation, procainamide was effective in establishing normal sinus rhythm.

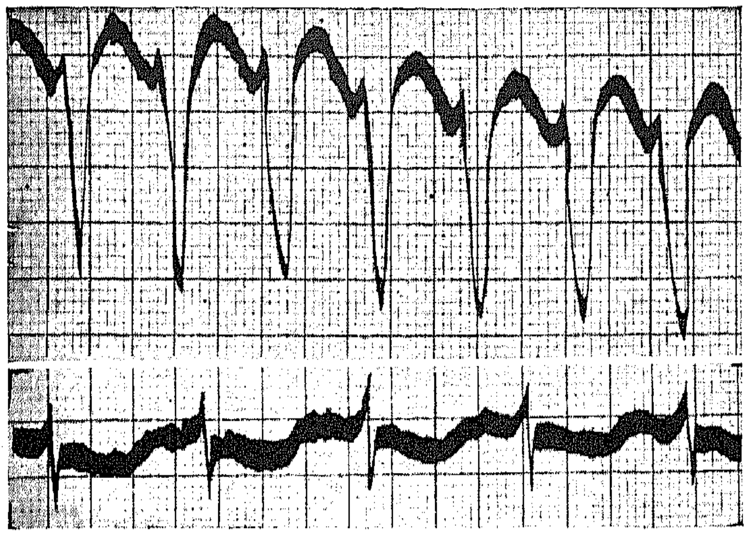

Fig. 41-2. *Upper*, Lead III; control tracing, ventricular tachycardia. *Lower*, Lead III; normal sinus rhythm with wandering pacemaker, after 1 gm. of procainamide intravenously. (From Research Service, Third New York University Medical Division, Goldwater Memorial Hospital, New York; and Department of Anesthesia, New York University-Bellevue Medical Center.)

Zapata-Diaz *et al.* (1952) called attention to the danger of the use of procainamide in atrial flutter owing to the possibility of a 1:1 atrioventricular response with aberrant intraventricular conduction. This may lead to ventricular flutter or fibrillation.

Woske *et al.* (1953) studied the relative sensitivity of atrial and ventricular tissue to the action of procainamide in the dog heart. They found the amide afforded complete protection of the heart against electrical induction of atrial fibrillation. Procainamide elevated the thresholds to stimulation in the atria and ventricles and depressed conduction in all parts of the heart. These investigators interpret their findings to indicate that procainamide owes its antiarrhythmic action to its capacity to depress the excitability of the myocardium rather than to the prolonging of the period of refractoriness.

Sadove *et al.* (1954) found procainamide to be useful in the treatment of pylorospasm in infants. The drug was used in place of the conventional antispasmodics and in cases where these had failed. Procainamide was administered orally in solution, 15 mg. every 6 hours. Sadove suggests that the success of the therapy is due to the local anesthetic action of procainamide on the gastric mucosa, resulting in a quiescence of gastrointestinal motility and relaxation of the pyloric sphincter.

Kjellin (1957) employed procainamide successfully in the treatment of a limited number of cases of dystrophia myotonica. Intravenous therapy was more effective than the oral administration.

Procainamide is recovered in the urine unchanged to the extent of 60 per cent of the administered dose. About 10 per cent is excreted as conjugated *p*-aminobenzoic acid.

The evidence is clear that procainamide is effective in the treatment of ventricular arrhythmias and tachycardia. It is apparently valuable also in atrial fibrillation of recent origin, but not in long-standing cases. The intravenous administration of procainamide must be done with caution: not faster than 100 mg. per minute. The dose is 200 to 1000 mg. Orally the drug is given in capsules of 0.25 gm. One to two capsules are given every 4 to 6 hours. The effect in ventricular tachycardia is shown in figure 41-2.

The untoward side effects are gastrointestinal distress and hypotension. The latter occurs more often upon intravenous administration. Inouye *et al.* (1951) observed 1 case of agranulocytosis in an 87-year-old man following maintenance therapy with procainamide.

Acute febrile responses have been observed in a few patients to whom procainamide had been given. In one case the temperature rose to 104°F. and returned promptly to normal after the drug was discontinued. Wasserman *et al.* (1959) conducted an extensive study on dogs with procainamide and antidotal measures for combating its toxic reactions. The toxic manifestations of procainamide were electrocardiographic changes, changes in electrolyte balance, and marked hypotension. Hypertonic sodium lactate solution was found to reverse these changes. When molar sodium lactate solution was combined with norepinephrine, previously irreversible manifestations of procainamide intoxication were promptly restored to normalcy or near normalcy.

Southworth *et al.* (1950) observed the antiarrhythmic activity of lidocaine. Harrison *et al.* (1963) used lidocaine in 12 patients undergoing cardiac surgery and compared it with procainamide. The parameters studied were arterial pressure, myocardial contractile force, and ventricular excitability. Neither agent caused a significant prolongation of the absolute refractory period. Each drug evoked an increase in the stimulation threshold during diastole. Lidocaine, 1 to 2 mg./kg., elicited no significant circulatory depression, but procainamide, 2 to 4 mg./kg. evoked a fall in arterial pressure and decrease in the contractile force of the right ventricle. These workers contend that lidocaine is the preferred drug. It will be interesting to see if others corroborate these findings.

## The Use of Drugs in Heart Block

Impairment of conduction of the wave of excitation from the atria to the ventricles through the A-V node and the bundle of His is termed *heart block. First degree block* is the state in which all atrial beats are followed by ventricular beats, but the passage of the impulse from the atria to the ventricles through the A-V node and the bundle of His is prolonged, *i.e.*, prolonged P-R interval. *Second degree block* refers to a more severe disturbance in which some of the atrial impulses do not penetrate the conducting system and excite the ventricular tissue. *Third degree* or *complete block* is that condition in which no atrial impulses reach the ventricles and the ventricles establish an idioventricular rhythm. In complete heart block the pulse rate is usually 45 or less The rhythm is regular, and the rate does not increase upon exercise. When the ventricular pause endures for 5 to 15 seconds, the patient experiences a feeling of light-headedness and syncope often occurs. Longer pauses known as Adams-Stokes attacks may cause convulsions and death.

**Atropine in heart block.** Because of the anticholinergic action of atropine on the cardiac vagus, the vagal control of the heart can be partially abolished. Thus, one would expect the drug to afford relief in heart block, which it does often in milder cases of first and second degree block. It is more successful in patients of the younger age group in whom vagal tone has not been diminished by the passing of the years. Most of the patients with heart block are of the older age group and suffer from some intrinsic heart disease. When atropine affords relief, it is usually in a younger person or one in whom some metabolic change in the myocardium has made the muscle transiently very susceptible to vagal influence. Thus, in the aberrant A-V conduction of the Wolff-Parkinson-White syndrome, the anomaly is readily reverted to normal by atropine. As a rule, 0.4 to 0.5 mg. of atropine sulfate is given 3 to 4 times daily.

**Sympathomimetic amines in heart block.** The various sympathomimetic amines are discussed in chapter 34. In larger doses, drugs like epinephrine and norepinephrine can produce ventricular arrhythmias, ventricular fibrillation, and death. However, when properly used in heart block, certain of these drugs are of distinct value in increasing the heart rate and cardiac output.

Of the various drugs in this class, isoproterenol (Isuprel) appears to be the most effective. Isoproterenol is capable of restoring heart beat in asystole, increasing the heart rate in severe bradycardia, and it may suppress the tendency toward fibrillation by stimulation of the S-A node.

The hemodynamics of the action of isoproterenol in heart block were studied by McGaff *et al.* (1959). The drug was given in linguets, 10 to 20 mg. There was an increase in cardiac output, usually with an increase in stroke volume and a decrease in peripheral resistance. Levinson *et al.* (1959) administered isoproterenol via a catheter into the main pulmonary artery. In 2 patients with heart block they observed a more rapid ventricular rate, unaltered stroke volume, increased cardiac output, unaltered oxygen consumption, decreased arteriovenous oxygen difference, and decreased total vascular resistance in the pulmonic and systemic circulations. In one patient sinus rhythm was restored.

**Isoproterenol and myocardial metabolism.** The inhibitory effects of isoproterenol on various types of smooth muscle as well as the stimulatory effects of the compound on myocardial contractile force and rate are considered as beta adrenergic receptor responses, page 562. Winterscheid *et al.* (1963) studied the action of isoproterenol on the carbohydrate metabolism of the isolated canine heart. They observed that oxidative metabolism increased significantly and proportionally to the heart rate. Glucose utilization was unaffected by isoproterenol; lactate utilization and excretion were increased slightly. The glycogen content of the heart was not significantly changed. Of special interest was the observation that doubling the optimal concentration of the drug evoked arrhythmias and A-V conduction defects. This last observation sounds a warning that with isoproterenol one is dealing with a dependable, potent agent with a narrow margin of safety.

The usual route of isoproterenol administration is the linguet of 10 to 20 mg. given several times a day. For emergency use 0.2 mg. may be given intramuscularly or subcutaneously. For more rapid action the drug may be given by intravenous infusion, 5 μg./min., until a satisfactory response is achieved.

Because of the necessity of frequent medication with isoproterenol linguets in heart block, sustained release tablets have been made available. Dack and Robbin (1961) used 30-mg. tablets every 4 to 6 hours. They reported that therapeutic results were achieved in most cases. Side effects consisted of tachycardia, palpitation, and tremor; these were few. In their opinion oral medication was less apt to produce tachycardia or angina than medication with linguets.

Isoproterenol appears to be replacing all other sympathomimetic amines in the treatment of heart block. The ease of medication, dependability, and relative freedom from adverse untoward effects mark isoproterenol as the drug of choice in this condition.

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# 42

# The Response of the Coronary Vessels to Drugs

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In the preceding chapters of this treatise we have frequently discussed the action of drugs on the coronary arteries as one of the aspects of their pharmacologic action. The organic nitrates and the inorganic and organic nitrites dilate the systemic arteries, and coronary vessels share this response. Papaverine, an alkaloid obtained from opium, elicits coronary dilatation. Ephedrine and Paredrine, both sympathomimetic drugs, produce coronary dilatation. In this chapter it is our purpose to consider the various pharmacologic agents which, because of their dilating action on the coronary vessels, are useful in the treatment of angina pectoris and coronary insufficiency and occlusion.

**The nature of coronary insufficiency.** The heart, in common with all other muscle, depends upon its blood supply for nourishment. This is supplied by the coronary arteries. When this is diminished, the mechanical efficiency of the myocardium as a pump is impaired. When the coronary artery blood supply to the heart is completely occluded, the muscle will die. The systolic pressure for the flow of blood through the coronary circulation is essentially the same as the aortic pressure since the coronary artery has its origin in the aorta.

An adequate blood supply to nourish the heart can be maintained only, if (1) the aortic pressure is sufficient; (2) the blood flowing through the coronary circulation provides the necessary nourishment; (3) the lumen of the coronary vessels is not narrowed by spasm or plaques; and (4)

they are not occluded by the presence of infarcts. With moderate decreases in aortic pressure the coronary circulation remains adequate; however, reductions in aortic pressure may embarrass the coronary circulation even if the vessels are normal. It is clear that a marked reduction in red cells in blood of the coronary circulation may so diminish the oxygen supply that myocardial hypoxia may prevail. However, the most prevalent causes of coronary insufficiency lie in the vessels, namely, narrowing of the lumen by spasm or by plaques on their intima (Krantz and Ling, 1958).

The formation of atherosclerotic plaques is not a disease of the aged, but the process appears to be continuous through life. In addition, another factor which is of paramount importance is the progressive thickening of the intima and elastica with respect to the passing of the years. At birth the intima is 6 μ, at 10 years 54 μ, at 35 years 124 μ and at 70 years 190 μ. This thickening of the intima, associated with the atherosclerotic process, results in the narrowing of the lumen of the coronary artery and a reduction of blood supply to the heart.

Coronary artery disease may produce death by three different mechanisms. The first is by self-electrocuting currents set up in the heart itself from differences in oxygen content in areas of the muscle that are in juxtaposition. The total coronary flow may be adequate to support the heart beat, but because of uneven distribution of the blood, caused by narrowing of the lumen of the arteries in localized areas, a state of electrical instability is produced. The second is caused by reduced arterial inflow, insufficient to sustain the beat of the heart. The third is by the destruction of the myocardium so that there is not enough contractile force to circulate the blood (Beck, 1958). The prevention of each of these conditions is dependent upon the patency of the coronary circulation and its capacity to supply adequate oxygen and nourishment to the heart.

**Pharmacologic experimental methods.** The pharmacologist is constantly on the alert for drugs which will exert a specific dilating action on the *coronary vessels.* Therefore, through the years he has developed methods experimentally to test the action of drugs on the coronary arteries. No attempt will be made to give a detailed description of all of the various experimental procedures. Some of the more recent methods that appear to be most significant will be discussed.

A simple procedure that provides a first approximation of the action of a drug on the coronary arteries was developed by Voegtlin and Macht (1913). A smooth muscle preparation consisting of rings joined in tandem fashion from the circumflex and descending coronary arteries of the steer is used. The authors have used this method many times to indicate whether or not a new chemical agent will cause the relaxation of the coronary arteries. Failure to relax the vessels in this simple experiment is usually indicative of lack of effective coronary dilatation with more complex procedures.

The Langendorff (1895) method with its modern refinements is used routinely for screening quantitatively coronary dilators. The rabbit's or kitten's heart is rapidly excised and perfusion of the coronaries is made by passing a specially prepared Locke-Ringer's solution through the aorta. The rate of perfusion of the solution containing the drug is used as a measure of the caliber of the coronary arteries.

Goodale *et al.* (1947) applied the nitrous oxide method of measuring blood flow to the measurement of coronary artery flow. The arteriovenous nitrous oxide differences are measured from femoral arterial blood and coronary sinus venous blood. The latter is obtained by catheterization of the coronary sinus. This method has been applied to the study of coronary flow in man by Bing *et al.* (1947). The results were found to correlate well with those obtained by other methods.

Leighninger *et al.* (1959) employed a procedure to measure the coronary artery supply to the ischemic myocardium and to evaluate drugs with respect to their capacity to increase the blood supply to the ischemic area. They ligated the circumflex or the descending ramus of the left coronary artery of the dog. This produced localized ischemia with its concomitant oxygen differential. By cutting the artery distal to the ligature and measuring the blood which escapes, they obtained a measurement of the blood in the arterial bed of the ischemic muscle. This "coronary back flow" comes into the circumflex artery by way of intercoronary arterial communications from the unoccluded coronary arteries. The arterial pressure was maintained at 100 mm. Hg, so that the "coronary back flow" was dependent upon the coronary arteriolar resistance. This is the factor upon which the coronary dilating drugs exert their effect. For example, the average "coronary back flow" is 4.4 ml./min.: 0.6 mg.

glyceryl trinitrate increased the back flow on the average of 0.88 ml./min. These investigators refer to this value as a "glyceryl trinitrate unit" with which other coronary dilating drugs may be compared.

Radioactive isotopes have been used to measure coronary flow in animals and man. Sevelius and Johnson (1959) used human albumin containing $I^{131}$. The solution is injected into an antecubital vein. The passage of the radioactive tracer through the heart is measured by a gamma ray detector placed on the chest wall over the outflow tract of the heart and measures the chronologic change in counting rate. Three peaks of radioactivity are observed, the third peak is related to myocardial blood flow, since it does not appear in dogs when the main coronary arteries are occluded. The values agree well with the nitrous oxide method, although the values were slightly higher. The advantage of the method is its rapidity and simplicity in the hands of investigators familiar with isotope technics.

Although no one method has been found wholly satisfactory, much progress has been made in overcoming the inaccuracies and unphysiologic conditions imposed by the earlier methods. The normal rate of flow to the heart appears to be about 60 to 70 ml./100 gm. of myocardium/minute. Coronary vasodilatation resulting from hypoxia and other causes is capable of causing a 3-fold or larger increase in the supply. A drug which would simulate the action of these metabolic products in effecting a relaxation of the smooth muscle of the coronary arterioles might serve as a pharmacologic agent for conditions of coronary insufficiency.

With these and many other experimental procedures available it is obvious that the question of whether or not a drug is a coronary dilator can be answered. In addition, the quantitative aspects of the procedures compare quite favorably with other biologic methods. The difficulty appears in correlating these laboratory measurements with the efficacy of the drug in coronary disease. Papaverine was shown to be the most efficient among a number of coronary dilators. Yet, clinically, the drug has been most disappointing. Our knowledge of a drug to be useful in coronary insufficiency must embrace the following components: (1) the effect of the drug on coronary outflow; (2) the effect of the agent on the ratio cardiac work/coronary flow; (3) the effect of the drug on the metabolism of the myocardium at a cellular level; and (4) the influence of the compound on the efficiency of the heart in its work performance. The approbation or disapprobation of a coronary vasodilator must come from its clinical trial on patients with coronary insufficiency.

## ANGINA PECTORIS

Angina pectoris is a disease which manifests itself in the form of dramatic and terrorizing post-sternal pain. It may last a period of several seconds, terminating in death, or it may return repetitiously over a period of several decades. Pain is the dominating symptom. It is startling and comes, as it were, out of a clear sky. The pain begins, as a rule, poststernally and is referred to the peripheral distribution of the eighth cervical through the fourth thoracic posterior roots. The pain manifests itself in the left shoulder and is referred over the flexor surface of the left arm to the tips of the medial fingers.

The disease was first described by Heberden (1768) before the Royal College of Physicians. A century later Brunton (1867), the distinguished English therapist, used amyl nitrite successfully in the treatment of the acute pain. Twelve years later Murrell (1879) found that the vasodilator glyceryl trinitrate was useful in effecting relief. Three-quarters of a century later we are still using the same drugs.

The etiology of angina pectoris is not clearly understood. It appears, however, that the poignant pain is the result of cardiac hypoxia. Furthermore, as the attack is often precipitated by effort it is considered to be due to the failure of the coronary vessels to dilate when the heart needs additional nourishment. The failure of the coronary arteries to dilate when an additional work load is imposed upon the heart may be due to the impeding effects of the atherosclerotic process. Raab (1962) proposes that a second mechanism may be incriminated; namely, an acute influx of catecholamines from the sympathetic nerve endings and adrenal medulla. He considers this impact upon the myocardium a "biochemical hypoxicating pain producing trigger mechanism." Regardless of the precise cause, cardiac hypoxia results. Although the future may shed new light on the etiology of the disease, the practical fact remains namely, that if the coronaries are acutely dilated by a drug the attack is usually terminated.

**The relief of acute pain.** Therapy in angina pectoris is predicated upon an etiology involving acute coronary constriction or the failure of the vessels to dilate when the heart needs extra nourishment. As the pain is excruciating, the value of a drug depends largely upon its promptness in producing coronary dilatation.

For the treatment of acute pain in angina pectoris, glyceryl trinitrate is the drug of choice.

## DRUGS OF THE NITRITE:NITRATE SERIES

**Sodium Nitrite, U.S.P.** Sodium nitrite occurs as a white to a slightly yellow granular powder. It also occurs in opaque, fused white masses or sticks. It is deliquescent in the air. One gram of sodium nitrite dissolves in 1.5 ml. of water.

Sodium nitrite is seldom used today in the treatment of angina pectoris or hypertension. Tolerance rapidly develops upon repeated dosage, and frequently sodium nitrite evokes a throbbing headache in patients. It has, therefore, been almost entirely replaced by other drugs of this series.

Sodium nitrite converts hemoglobin into methemoglobin. Owing to the formation of methemoglobin by nitrites, the nitrites have been found useful in the treatment of cyanide poisoning. In cyanide poisoning the methemoglobin unites with the cyanide ion, forming cyanmethemoglobin which is comparatively innocuous. Therefore, the cytochrome oxidase which would otherwise have been attacked by the cyanide ion is spared. It is for this purpose that sodium nitrite is recognized in the U.S.P.

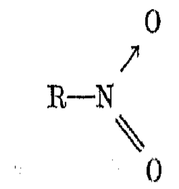
**The organic nitrates.** Although the nitrate ion does not elicit any distinctive pharmacologic response, certain organic nitrates act as potent vasodilators. The chemical structure and classification of these substances may be seen from the accompanying formulas.

$(NaNO_2)$

Sodium
Nitrite

$(NaNO_3)$

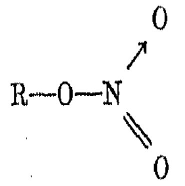
Sodium
Nitrate



Nitro
Compounds

$(R—O—N{=}O)$

Organic
Nitrites



Organic
Nitrates

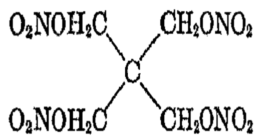
The substances of interest in this class of organic nitrates are glyceryl trinitrate, erythrityl tetranitrate, and pentaerythrityl tetranitrate. The structures of these substances are shown in the accompanying formulas.

$C_3H_5(NO_3)_3$

Glyceryl Trinitrate, U.S.P.

$C_4H_6(NO_3)_4$

Erythrityl Tetranitrate



Pentaerythrityl Tetranitrate
Peritrate

For many years it was assumed that the organic nitrates, such as those mentioned in the foregoing paragraph, owed their vasodilating action to the fact that in the body they were hydrolyzed to form nitrate. This in turn was reduced to nitrite, and the nitrite ions produced the response. Krantz *et al.* (1940) showed that the organic nitrates produced a depressor response by virtue of their own molecular structure and not through hydrolysis and reduction to nitrite. Furthermore, if one considers the marked activity of glyceryl trinitrate, which in doses of 0.06 mg., causes a fall in blood pressure in man, while sodium nitrite requires a dosage of at least 60 mg. to elicit a typical depressor response, it seems most unusual that the action of the organic nitrate is dependent upon nitrite formation. It therefore appears that these substances elicit a depressor response by virtue of their specific chemical constitution.

Further evidence of the direct action of the organic nitrate molecule was produced by Krantz *et al.* (1962). When glyceryl trinitrate was perfused through the coronary vessels of a rabbit's heart, only a minute fraction of the effective dose was converted to nitrite. Neither organic nor inorganic nitrite in levels found in the perfusate evoked coronary dilatation.

Hepple and Hilmoe (1950) isolated an enzyme from hog's liver which catalyzes the reduction of glyceryl trinitrate to glyceryl trinitrite by glutathione. Glutathione appeared to react with glyceryl trinitrate to form trinitrite before hydrolysis occurred. The reaction of glyceryl trinitrate with glutathione is an orderly time process, whereas the vasodilatation response to glyceryl trinitrate is almost immediate and quite evanescent. As glyceryl trinitrite is very unstable and is decomposed immediately by water and air, evidence indicates that the vasodilatation response of glyceryl trinitrate is due to the intact molecule and not to its reduction product or its products of hydrolytic cleavage.

Hunter *et al.* (1953) demonstrated that inorganic nitrites and organic nitrates such as glyceryl trinitrate and mannitol hexanitrate inhibited oxidative phosphorylation in liver mitochondrial preparations. Krantz *et al.* (1951 *et seq.*) showed that these agents inhibited arterial ATPase activity. Whether or not these enzymic effects of the nitrite-nitrate series are associated with their vasodilatation activity remains to be established.

**Glyceryl Trinitrate, U.S.P. (Nitroglycerin).** This compound is used more than any other drug in the treatment of the acute anginal attack. The compound evokes vasodilatation. The coronary vessels share this action of the drug with the systemic arterial system. The drug acts on the musculature of the vessels directly, irrespective of their autonomic innervation.

In the treatment of the acute attack of angina the drug should always be readily available to the patient. Glyceryl trinitrate may be carried in a convenient container in the form of small, readily-soluble tablets 0.4 to 0.6 mg. The attack is often preceded by an aura or premonition. The terror of impending death is one of the psychic features of the disease. The tablet is promptly placed under the tongue upon the first indication of an oncoming attack. The drug effect comes on promptly, as a rule, within 1 to 3 minutes. In most instances the drug affords prompt relief. The action of glyceryl trinitrate is evanescent. According to Leighninger *et al.* (1959), the duration of effect on the ischemic myocardium lasts about 5 minutes.

In many persons the blood pressure falls sufficiently to produce headache and throbbing in the temples. It is advisable if this occurs to direct the patient to expel from the mouth the undissolved tablet just as soon as relief as been effected. Rest and relaxation after the use of the drug are also desirable. In other individuals it may be advisable to use a smaller dosage of the drug routinely, such as 0.3 mg. Nevertheless, it appears that as the symptoms of an untoward nature with 0.6 mg. are not so severe and in most instances transient, the danger of undermedication is more serious than that of full glyceryl trinitrate dosage. When glyceryl trinitrate tablets are swallowed instead of administered sublingually, their action is often erratic and ineffective (Riseman *et al.*, 1958). The tablets of glyceryl trinitrate are stable for many years, providing they are not exposed to elevated temperatures. The ester is volatile, and the tablets rapidly lose the active ingredient when kept in a warm place.

The frequency of moderate or marked response to glyceryl trinitrate, other generally used organic nitrates, and sodium nitrite when administered orally, sublingually, and subcutaneously is shown in figure 42-1.

Berry and Roach (1958) used blood levels of nitrate to determine the absorption of organic nitrates. Normal blood nitrate levels averaged 4.8 $\mu$g./ml. After sublingual administration of 1.2 mg. of glyceryl trinitrate, they rose to 8.4 $\mu$g./ml. in 4 minutes, remained at that level for 10 minutes and were approximately normal at 15 minutes. These data correlate well with our knowledge of the response to the drug in patients with coronary insufficiency.

The mechanism of action of glyceryl trinitrate in coronary artery insufficiency has not been clearly understood. Raab (1962) proposed that it antagonizes the hypoxic effect of the release of catecholamines from the sympathetic nerves and adrenal medulla on the myocardium. Honig *et al.* (1960) considered that it relieves the cardiac ischemia by enhancing the delivery of oxygen to the myocardial cells. Krantz *et al.* (1953) showed that glyceryl trinitrate inhibited arterial ATPase and suggested that this action might be associated with the vasodilating effect. Needleman (1964) demonstrated that glyceryl trinitrate enhances the utilization of glucose oxidation in slices of the rabbit's heart. It is clear that much needs to be done to provide a satisfactory explanation of the action of a drug that has enjoyed almost a century of dependable use.

Sustained release tablets of glyceryl trinitrate are available for prophylactic treatment in coronary insufficiency. These tablets contain 6.4 mg. of glyceryl trinitrate (Nitroglyn) and are useful in providing sustained glyceryl trinitrate medication over a 6- to 8-hour period (Jablons *et al.*, 1956).

A severe shock-like syndrome was reported by Jacobson (1950) in a patient who ingested whiskey and followed it by a sublingual tablet of glyceryl trinitrate. The patient had previously used the drug routinely without untoward effects.

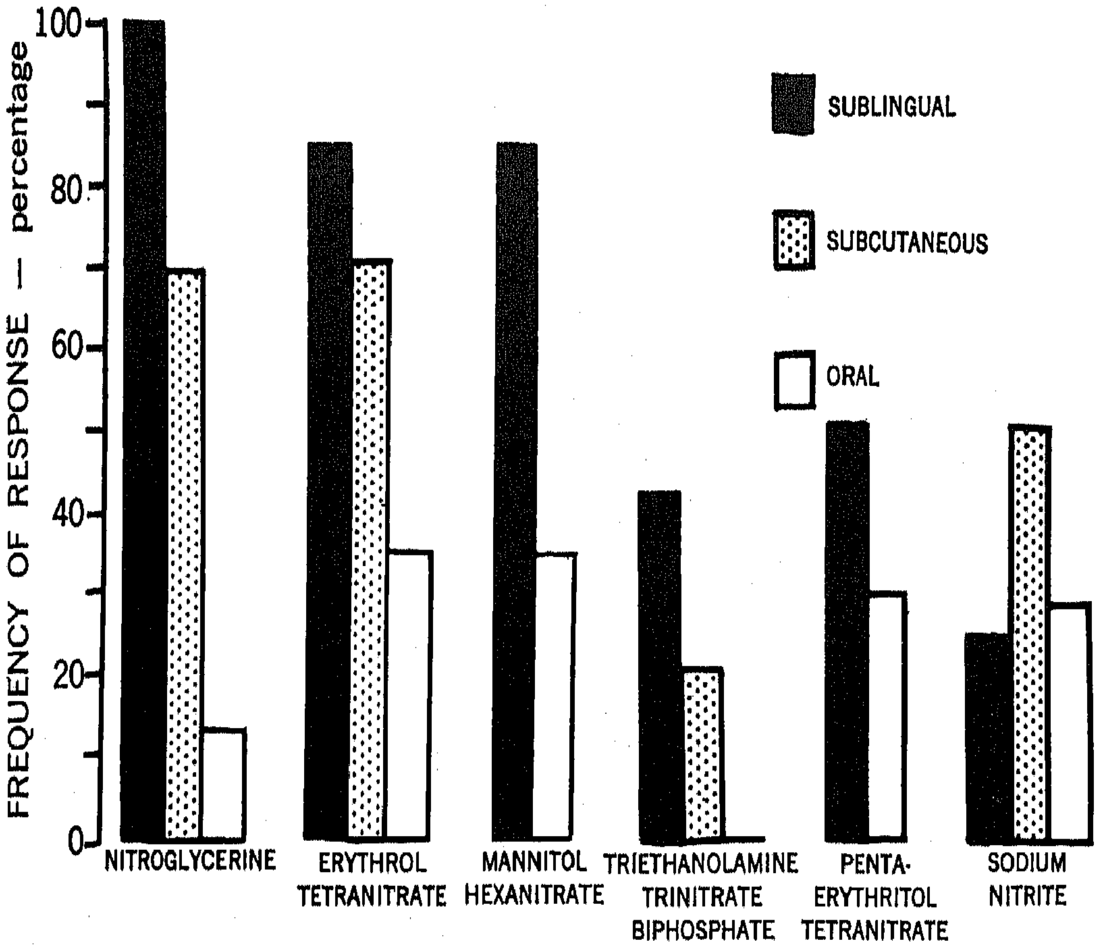


FIG. 42-1. Response of organic nitrates. (From J. E. F. Riseman, G. E. Altman, and S. Koretsky: Circulation, 17: 22, 1958).

We have become aware of other individuals who after the inhalation of volatile organic nitrites experienced vertigo, faintness, flushing, and pallor upon the ingestion of alcohol. It seems prudent to space widely the intake of these 2 vasodilators.

**Amyl Nitrite, U.S.P.** This ester is an oily, clear, faintly yellowish liquid with a strong characteristic odor. The odor resembles that of amyl alcohol and is quite objectionable to many people. The vapor pressure of amyl nitrite is relatively high, 53 mm. at 24°C. The high vapor pressure permits the drug to be used by inhalation. The vapor of amyl nitrite mixed with air or oxygen is explosive. All sources of flame must be removed during inhalation.

The compound is available in ampules of glass (pearls) which are easily crushed. The containers are enclosed in a fabric which lessens the possibility of cutting one's fingers upon the fracture of the glass. At the appearance of a premonitory symptom, the ampul is placed in a handkerchief and crushed. The handkerchief is held near the nostrils and the emanating vapor is inhaled. Relief is prompt. It occurs, as a rule, within 1 minute.

When the ampule is crushed, generally a mild explosive report occurs owing to the escape of vapors which form during the slow decomposition of the ester. This may be alarming to the uninitiated. In addition, the odor is very disagreeable and frequently causes a feeling of vertigo and faintness. The whole procedure is somewhat dramatic and besides, fills the room with the vapors of the drug.

**Alcohol.** A great number of investigators have studied critically the possible value of alcohol in coronary insufficiency. Our experience with the coronary vessels of the isolated heart of the rabbit leads us to the opinion that alcohol in blood levels acquired by drinking, or in higher concentrations, fails to dilate the coronaries. Russek *et al.* (1950) administered 1 to 2 ounces of whisky to anginal patients 5 to 30 minutes before the performance of a standard exercise test. The alcohol failed to prevent the transient electrocardiographic changes (RS-T depressions and T-wave changes) which were observed in the patients undergoing control tests. In sharp contrast, 0.4 mg. of glyceryl trinitrate prevented or significantly modified the previous patterns of cardiac ischemia. Alcohol, however, appeared to be as effective as glyceryl trinitrate in preventing the occurrence of anginal pain induced by the test. It appears that the role of alcohol in angina is not one of producing coronary dilatation, but that of a promptly-acting analgesic which increases the pain threshold. It is apparent, therefore, that alcohol may be objectionable in masking the danger signal "pain" of cardiac ischemia and may give rise to a false euphoria in the anginal patient.

### Routine Therapy in Angina Pectoris

There are many drugs used routinely in anginal patients as prophylactics against the acute attack. These drugs are mainly sedatives and vasodilators which are less acute in their action than those previously discussed.

**Sedatives.** The judicious use of sedatives may be of great value in the routine treatment of angina pectoris. The allaying of apprehension and the acceptance of a daily routine in which peace of mind and tranquility exist are helpful to the anginal patient.

*Phenobarbital* is also employed with much success. This drug is administered for mild sedation, 32 mg. 3 or 4 times a day. If insomnia is a factor, a shorter-acting barbiturate such as *pentobarbital* or *secobarbital* may be used just prior to retiring. For this purpose 100 mg. of either substance is usually a satisfactory dose.

Meprobamate, page 511, is being used with much success as a tranquilizing agent in angina pectoris and in postcoronary conditions. It produces less drowsiness than does phenobarbital and quells anxiety. Meprobamate is frequently mixed with routine vasodilators such as pentaerythrityl tetranitrate (Equanitrate) in the treatment of coronary insufficiency.

### Routine Use of Vasodilators

The xanthine derivatives, page 471, are useful vasodilators. The coronary vessels share this dilatation. Of the 3 xanthine derivatives used in medicine, as was stated previously, *theophylline* is the drug of choice for coronary dilatation.

**Theophylline, U.S.P.** Theophylline is a white crystalline powder. It is stable in the air and evokes a bitter taste. The compound is sparingly soluble in water (1 to 120) but freely soluble in solutions of alkalies with which it combines to form salts. The general pharmacologic responses of theophylline are similar to those of caffeine, page 471. Theophylline is less active as a cerebral stimulant than caffeine, but more powerful than caffeine as a coronary dilator and as a diuretic.

Using paper chromatographic procedures, Weinfeld and Christman (1952) observed that both 1-methyl and 1,3-dimethyluric acids were excreted in the urine after the administration of theophylline. Cornish and Christman (1957) identified another metabolite, 3-methylxanthine.

Theophylline is more frequently employed in the form of soluble derivatives or mixtures. The most popular of these is aminophylline, which is *theophylline* and *ethylenediamine*. The ethylenediamine renders the compound soluble and effects a more dependable absorption from the gastrointestinal tract.

Other solubilized theophylline dosage forms are *Theophylline Sodium Glycinate, N.F.*, *Theophylline Sodium Acetate, N.F.*, *theophylline isopropanolamine* (*Theopropanol*), *theophylline methylglucamine*, (*Glucaphylline*), *theophylline monethanolamine* (*Monotheamin*), *dihydroxyropyl theophylline* (*Hyphylline*), and *theophylline cholinate* (*Choledyl*).

One of the disadvantages of the various theophylline preparations is the gastrointestinal distress which they cause in a large number of individuals. This becomes particularly manifest when the dosage levels are increased. Indeed, this is unfortunate because it hampers intensive therapy with the drug and a more complete exploration of its possible benefits.

Theophylline can be shown to be a definite dilator of the coronary vessels in laboratory animals. Eckenhoff and Hafkenschiel (1947) placed aminophylline second on their list of coronary dilators, when viewed from its capacity to increase the nutritional aspects of the myocardium and aid in the energy conversion necessary for the heart cells to perform their maximal work. It would appear, therefore, that theophylline preparations would be routinely useful in angina pectoris. Of special interest is the work of Rall and West (1963), who studied the action of theophylline on the inotropic effect of norepinephrine on the segments of electrically driven rabbit's atria. In high dilutions of theophylline ($10^{-3}$ M) the action of norepinephrine was increased 8-fold. They interpret their findings to indicate that theophylline inhibits cyclic 3′,5′-nucleotide phosphodiesterase and prolongs the action of adenosine 3′,5′-phosphate, which is the mediator of the action of norepinephrine.

There is no unanimity of clinical opinion with respect to the value of theophylline in coronary insufficiency. It is our opinion that the limitation of the dosage, owing to gastrointestinal symptoms, and the assumption that absorption is complete is likely to be responsible for variations in

results observed by various investigators. Truitt *et al.* (1947) developed a comparatively simple method for estimating theophylline blood levels. In exploratory tests they found that the blood levels of theophylline varied greatly in different individuals on the same dosage schedule. The availability of such a test may prove very helpful in placing the therapy with theophylline on a more scientific and satisfactory basis.

Other methods for the estimation of blood levels of theophylline have been developed by Schack and Waxler (1949). Truitt *et al.* (1947) and Waxler and Schack (1950) studied blood levels of theophylline in patients when administered under various conditions. Truitt *et al.* found that approximately 0.5 mg. per cent is necessary for active diuresis. They observed excellent absorption from the administration of plain tablets (not enteric coated). A retention enema yielded blood levels comparable to those obtained by intravenous injections. Schack and Waxler demonstrated that theophylline did not enter the human red blood cell, and from animal experiments their data indicate that theophylline remains in the extracellular compartment of the body.

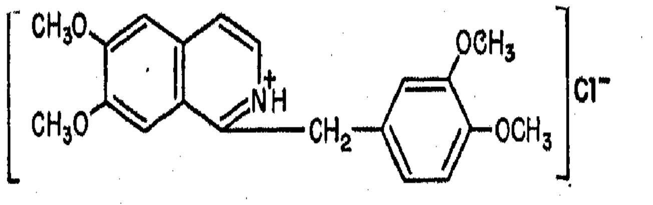
Theophylline unites readily with the sodium salt of the amino acid glycine. The combination was studied by Krantz *et al.*, 1947. It is less alkaline than the usual theophylline preparations and is usually well tolerated in the gastrointestinal tract. Paul and Montgomery (1948) used the product "Theoglycinate" in the treatment of patients with coronary disease and were able to give up to 2 gm. of theophylline in a day without gastric distress. Russek (1963) found that theophylline sodium glycinate in a hydroalcoholic elixir (Synophylate) was well tolerated and rapidly absorbed. It was capable of controlling symptoms and also of altering the electrocardiagraphic pattern after exercise. He preferred the elixir to the tablets because of better gastric tolerance.

Russek (1960) studied the effect of theophylline in a series of patients with anginal pain and controlled his observations by adequate placebo administration. The theophylline was given in elixir form (Elixophyllin), containing 80 mg. of theophylline in 15 ml. of the 20 per cent alcoholic elixir. He found the preparation strikingly effective in controlling the symptoms of angina, and also in modifying favorably the electrocardiographic response to standard exercise. He is of the opinion that inadequate absorption and limitation of dosage owing to gastric intolerance are likely responsible for the doubtful benefits achieved with other theophylline preparations. He further strengthens his conclusions by calling attention to the unequivocal value of aminophylline when administered intravenously. Russek's patients received 240 mg. of theophylline 3 times daily. It would have been of interest to have determined the blood-levels of theophylline in the patients during the medication. This method of theophylline administration appears worthy of further exploration.

It is our opinion that the drug, in one of its dosage forms, is warranted routinely in angina and postcoronary conditions. The pharmacologic basis for its use is sound. The drug is comparatively nontoxic, and side effects of an untoward nature are not so severe. It appears that Russek (1963) concurs in this opinion. He states, "These drugs (theophylline derivatives) can no longer be categorized as 'undesirable' or 'malignant' coronary vasodilators. These drug preparations should be more fully explored to permit their increased use in the management of coronary heart disease."

Aminophylline is generally prescribed in tablets 0.2 gm. 3 or 4 times a day. Aminophylline contains about 75 per cent of theophylline. The compound is also available intravenously and intramuscularly.

**Papaverine Hydrochloride, U.S.P.** Papaverine hydrochloride is the salt of an alkaloid obtained from opium or prepared synthetically. It is a member of the isoquinoline group of opium alkaloids, page 370. Papaverine hydrochloride occurs as a white crystalline powder. It evokes a bitter taste. One part of the salt dissolves in 30 parts of water. The structure of papaverine hydrochloride is shown in the accompanying formula.



Papaverine Hydrochloride, U.S.P.

Papaverine, although found in opium, is not related to morphine chemically or pharmacologically. It is not a narcotic like morphine. It does, however, elicit mild analgesic action. Papaverine does not evoke tolerance or addiction.

The drug can be shown to dilate the coronary vessels in laboratory animals. Measured by the critical evaluation of coronary dilators by Eckenhoff and Hafkenschiel (1947), this drug heads the list in efficacy. Indeed, clinical experience with the drug in coronary insufficiency does not parallel these findings. Its value clinically appears to be quite limited. Germane to this subject is the comment of Russek (1960), "Although papaverine was also found to exert benefit, the high dosage required, as well as the associated side effects from the drug, have precluded its use in routine management."

Axelrod *et al.* (1958) showed that papaverine is completely absorbed from the gastrointestinal tract of man. It undergoes almost complete metabolic alteration; only negligible quantities are excreted in the urine unchanged. The biologic half-life period in man is about 100 minutes. About 60 per cent of the dose of papaverine is excreted as glycuronide conjugates of phenolic metabolites.

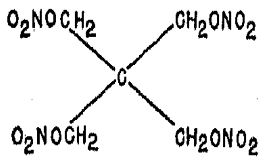
Katz (1941 *et seq.*) found that papaverine will cause the cessation of fibrillation of the heart similar to quinidine.

In view of the difference between the performance of papaverine in favorably affecting coronary flow in laboratory experiments and its frequent ineffectiveness in clinical trial, the action of the drug needs further study. Are the coronary flow increases due to an increased work load imposed upon the heart? What is the effect of the compound on cardiac metabolism at an enzyme level? Answers to these questions may be helpful in explaining the foregoing difference.

**Ethaverine.** Ethaverine is the ethyl analog of papaverine. The action of Ethaverine is similar to that of papaverine. The use of this drug in coronary insufficiency is quite limited. For a discussion see page 1033 of the 5th edition.

**Pentaerythrityl Tetranitrate (Peritrate).** The compound is an extensively used vasodilator of the nitrate series. Its structure is shown in the accompanying formula.

The compound is a white crystalline powder which is insoluble in water.



Peritrate
(pentaerythrityl tetranitrate)

Peritrate elicits a pharmacologic response similar to glyceryl trinitrate. Its action as a vasodilator is far less marked than that of glyceryl trinitrate. It is used routinely as a prophylactic coronary dilator in angina pectoris. It reduces the amount of glyceryl trinitrate required by anginal patients. The use of the drug increases the exercise tolerance of anginal patients. Reports in the literature of the use of Peritrate indicate that the drug has a definite place in the treatment of coronary insufficiency.

Lumb and Hardy (1963) explored the action of Peritrate by inducing gradual occlusion of the right coronary artery in each of 60 pigs. Half of the animals were given Peritrate orally in doses comparable to the human dose; the other half remained untreated. Death occurred in 83.3 per cent of the untreated animals and in 36.7 per cent of the treated animals after 5 weeks of the coronary occlusion. Radiopaque material injected into the left coronary artery demonstrated that collateral circulation was developed in the treated animals. This work corroborates the work of Zoll and Norman (1952) using sodium nitrite mentioned on page 675.

Russek *et al.* (1955) evaluated several coronary dilators in coronary patients using the Master 2-step exercise test. They found Peritrate to be the most effective agent in preventing electrocardiographic changes and the pain syndrome. They prefer Peritrate for prophylactic treatment.

Berry and Roach (1958) observed that Peritrate was capable of elevating the blood levels of nitrate in patients in a similar manner to glyceryl trinitrate. Sustained high blood levels of nitrate of about 7 μg./ml. were obtained when Peritrate was administered 4 times daily in 10-mg. tablets. Blood levels as high as 13 μg./ml. were achieved when the dosage was doubled. There were peaks of nitrate blood levels after ingesting the tablet which fell considerably prior to the taking of a second tablet. Sustained high blood levels of nitrate were observed when the patients were given 30 mg. of Peritrate every 12 hours in "timed-disintegration" (sustained release) capsules.

Riseman *et al.* (1958) found little difference in the therapeutic response to Peritrate whether it was administered orally or sublingually. They observed a greater tolerance to exercise tests after sublingual administration. They state, "This drug was only of moderate value in the treatment of patients with angina pectoris."

The question of therapeutic effectiveness and blood levels of nitrate may well be posed. The methods available determine total $NO_3^-$ as inorganic nitrate and as ester. Only the latter is therapeutically effective (Krantz *et al.*, 1940). The rapidity of hydrolysis of the ester in the blood is likely the determining factor in the degree and duration of response.

Tolerance to Peritrate does not readily develop. The side effects are *headache*, *lethargy*, *gastrointestinal disturbance*, and occasionally *visual disturbance*. Seldom are these side effects sufficiently severe to necessitate the withdrawal of the drug.

The usual dosage range of Peritrate is 10 to 20 mg. (1 or 2 tablets) 3 to 4 times daily.

**Triethanolamine Trinitrate (Metamine, Nitretamine).** This organic nitrate is available as its diphosphate salt as shown in the formula.

$$N(C_2H_4ONO_2)_3 \cdot 2H_3PO_4$$

Triethanolamine Trinitrate Diphosphate

This compound occurs as a white crystalline powder which is sparingly soluble in water.

Triethanolamine trinitrate is a potent dilator of the coronary vessels. Its action is similar to that of glyceryl trinitrate but more sustained. Melville and Lu (1951) observed that the molecule of triethanolamine trinitrate is more refractory to hydrolysis than is glyceryl trinitrate. This is likely a factor in providing a more sustained action.

Triethanolamine trinitrate has been used by numerous investigators to assess its value in the treatment of coronary insufficiency. In general, the clinical response to the drug is good. For example, Fuller and Kassel (1955) found the compound valuable in 82 per cent of a series of 71 patients in preventing anginal attacks. They believe it to be the most effective coronary dilator. There is no general agreement among clinicians with regard to the most effective of these coronary dilators.

Riseman *et al.* (1958) found metamine more effective sublingually than when given orally. Stomatitis was produced by sublingual administration. They state, "Headache was not experienced; this suggests that its vasodilating action is comparatively weak."

Tolerance to triethanolamine trinitrate appears to be rare. Untoward effects encountered are *headache*, *gastric pain*, *vomiting*, *dizziness*, and *palpitation*. Like other organic nitrates the compound is contraindicated in glaucoma.

Triethanolamine trinitrate in the form of its diphosphate salt is available in 2-mg. tablets. The usual daily dose is 4 to 5 tablets spaced throughout the day. In the acute attack glyceryl trinitrate should be used.

**Isosorbide Dinitrate (Isordil).** Isordil is 1,4,3,6-dianhydro-sorbitol-2,5-dinitrate. It is a white crystalline powder that is sparingly soluble in water. This organic nitrate was synthesized and studied pharmacologically by Krantz *et al.* (1940). Its use in the treatment of hypertension was investigated. It appeared to offer little advantage over other well established organic nitrates such as mannitol hexanitrate.

Sherber and Gelb (1960) reevaluated the drug in the treatment of coronary artery insufficiency. These investigators were favorably impressed by the clinical effectiveness of Isordil. Krantz *et al.* (1940) observed greater refractoriness of Isordil to hydrolysis as compared to other nitrate esters such as Peritrate and mannitol hexanitrate. Thus, Isordil provides longer periods of blood levels of the unhydrolyzed ester. Russek (1963) found that Isordil was the only coronary vasodilator which exerted a potent action when administered either orally or sublingually. The onset of action orally is about 30 minutes after ingestion; sublingually the action begins within 3 to 5 minutes.

Isordil is effective in the relief of coronary artery insufficiency symptoms within a period of 15 to 30 minutes. Of special note is the persistence of action, which extended over 4 to 5 hours. In a series of patients, the use of Isordil 10 mg. 4 times daily curtails drastically the use of glyceryl trinitrate and in some patients eliminates it completely. It is clear that prophylactic treatment in coronary insufficiency with organic nitrates is an established clinical procedure. As yet, however, the drug of choice, remains to be established.

**Erythrityl Tetranitrate (Cardilate).** This compound is another typical organic nitrate that was formerly used in hypertension. The compound was administered orally, and its effectiveness was comparable to other drugs of this class such as mannitol hexanitrate. Its relative value in coronary artery insufficiency has been established by various investigators, and the present interest appears to stem from the fact that it is active when administered sublingually. The sublingual effect occurs within 5 minutes; orally the effect requires 30 minutes. The relative effectiveness of erythrityl tetranitrate is shown in figure 42-1. The drug is available in 5-, 10-, and 15-mg. tablets. Up to 30 mg. daily in divided doses is well tolerated.

**Monoamine oxidase inhibitors.** The monoamine oxidase inhibitors in the treatment of mental illness have been discussed on page 518. They have been used in the treatment of coronary insufficiency. Among the drugs employed are iproniazid (Marsilid), isocarboxazid (Marplan), and phenelzine dihydrogen sulfate (Nardil). Their effectiveness in coronary insufficiency disease is polemic. They are not potent coronary artery dilators. The most effective agent iproniazid (Marsilid) has been withdrawn from the market because of toxic side effects. Russek (1960) compared the effects of Marplan, Nardil, Niamid, and Tersavid and observed that a decreasing incidence of effectiveness varied with a declining frequency of side effects.

The side effects of the monoamine oxidase inhibitors are discussed on page 518. It is clear that these might be serious in some cases. Therefore, the indiscriminate use of these drugs in coronary insufficiency should be enjoined. Furthermore, the elevation of mood effect, with a concomitant unawareness of the danger signals in the disease, must be carefully considered in the use of monoamine oxidase inhibitors. From the data available the indication appears that their principal benefit is psychic in character, and their role as specific coronary dilators relieving cardiac ischemia remains to be established. For a more detailed discussion see page 1037, 5th edition.

**Miscellaneous coronary artery dilators.** Some new types of chemical structures have been found to be coronary artery dilators. One of these is dipyridamole, Persantin; chemically it is 2,6-bis(diethanolamino)-4,8-dipiperidine-pyrimidino-(5,4-d) pyrimidine. Charlier (1961) in his table of comparative coronary dilating effects of various drugs lists Persantin as an agent with little potency. Some clinical investigations with Persantin in coronary insufficiency appear favorable; on the other hand, Foulds and Mackinnon (1960) in a carefully controlled series of patients found it no better than a placebo. Kinsella *et al.* (1962) found no benefit from Persantin in doses up to 100 mg. daily. Larger dose levels (225 mg. daily in anginal patients) induced gastrointestinal symptoms in some patients. The value of the drug remains to be established. Persantin is available in 25-mg. tablets.

Another compound available in Europe, but not as yet in the United States, is Amplivix. Chemically the agent is ethyl-2-(diiodo-3′,5′-hydroxy-4′-benzoyl(-3-benzofuran. Charlier (1961) classifies Amplivix as the most potent of all the common and rare coronary dilators. Its potency is given as 1 compared with 0.3 for glyceryl trinitrate. For an account of its pharmacologic response and early clinical studies which appear to be promising, see Charlier (1961). As indicated previously, potency as a coronary dilator experimentally is not always indicative of therapeutic success.

**Surgical procedures.** The aim of surgical procedures in coronary insufficiency is to relieve as far as possible the adverse effects of diminished coronary flow. The procedures generally employed are: denervation of the heart; improvement of the circulation of the myocardium, or reduction of the metabolic demands of the heart on the coronary circulation by thyroidectomy (Hellerstein, 1957). In place of thyroidectomy, propylthiouracil (page 887) has been used with limited success. Blumgart and Freedberg (1952) employed radioactive iodine in patients with coronary insufficiency for the purpose of reducing thyroid activity and consequently the oxygen requirement of the myocardium. The number of patients suited for this type of treatment with radioactive iodine is small.

## CORONARY INSUFFICIENCY AND OCCLUSION

**The nature of coronary occlusion.** The presence of coronary occlusion may be demonstrated in about 40 per cent of all autopsies in males above the age of 50. There is a definite hereditary predisposition. In younger individuals the prognosis is more serious. This is possibly due to the poor development of collateral circulation in younger individuals.

Coronary insufficiency produces cardiac hypoxia, and the hypoxic state may produce anatomic changes in the myocardium. Fibrosis of the myocardium may result, and compensatory hypertrophy take place. The hypoxic state of the heart may encourage the development of interarterial anastomotic channels of collateral circulation. This may afford protection against coronary occlusion. It generally requires about 2 weeks for the collateral circulation to become adequate. Thus, slow occlusions permit time for the development of collateral circulation, and myocardial damage is minimal. Sudden occlusion, however, does not provide the time interval for collateral circulation, and infarction follows.

Many individuals with coronary occlusion have an elevated serum lipid level. The serum phosphorus level, however, is not proportional to the elevated cholesterol level, *i.e.*, there is an increase in the cholesterol-phospholipid molar ratio. This ratio is apparently the important factor. The diminished level of the phospholipid emulsifiers does not adequately maintain the colloidal suspension of cholesterol. Cholesterol and fat deposits in the arterial lumen contribute to the coronary atherosclerosis. In addition, Gofmann *et al.* (1950) showed the presence of large, low-density lipoprotein molecules in the serum of patients with coronary occlusion. This also may be a component in the etiology of the disease. Gertler *et al.* (1950), considering a number of factors predisposing one to coronary artery disease, found the highest correlation between coronary artery disease and total serum cholesterol levels. The reduction of serum cholesterol levels is discussed on page 956.

In addition to the significance of cholesterol in the pathogenesis of coronary artery lesions, the anatomic and physiologic condition of the arterial tissue undoubtedly plays an important role. Thannhauser (1952) states: "The mechanism of cholesterol accumulation in the arterial tissue can not be explained by a one-sided investigation of the physical properties of the lipid constituents and their protein aggregates (lipoproteins) in the plasma. The anatomic and physical properties of the arterial tissue are of equal importance in the accumulation of cholesterol in this tissue."

The use of drugs in coronary occlusion follows the general pattern set forth in the foregoing paragraphs. There is no substitute for morphine in the control of the pain of the immediate attack. Its action is mainly upon the cerebral centers. It is doubtful if the drug in therapeutic doses causes appreciable coronary dilatation.

The urgency of the acute coronary attack frequently provokes the use of other measures also. Oxygen inhalation is indicated. The slow intravenous injection of aminophylline, 0.5 gm., or papaverine hydrochloride, 100 mg., is frequently used.

The long period of rest, the nursing care, the interdiction of tobacco, and the diminished activity after the patient becomes ambulatory are not within the purview of this treatise. However, the question of routine medication is a consideration.

**Vasodilators in coronary occlusion.** The use of strong vasodilators such as the organic nitrates may prove harmful if the blood pressure is low. Glyceryl trinitrate is withheld until the blood pressure has increased to an approximately normal level. The pressor amines may be employed to increase the systemic arteriolar resistance. Methoxamine (Vasoxyl), page 556, is one of these drugs which appears to be favored; it elicits a pressor effect uncomplicated by a myocardial action. It is effective intramuscularly in intermittent doses (Selzer and Rytand, 1958).

Theophylline preparations may be safely employed routinely. To increase the prothrombin time of the blood, bishydroxydicoumarin may be used, page 702. For routine sedation, phenobarbital or meprobamate appear to be the drugs of choice. Rest, relaxation, tranquility of mind, and diet appear still to be far more essential than drugs.

The use of drugs which dilate the coronary vessels routinely in cases of coronary occlusion appears to be a means for decreasing the damage that the myocardium may have suffered from the occlusion. Bishydroxydicoumarin has been shown to dilate the coronary vessels. It is highly probable that the coronary dilating action of this drug is a facet in its beneficial effect in coronary occlusion. It seems reasonable indeed that increasing the blood supply to the infarcted area would decrease further damage and aid in the repair process of the damaged areas of the myocardium.

The use of vasodilator drugs routinely in coronary occlusion is predicated upon their effectiveness in increasing coronary flow and aiding in establishing collateral circulation. This should not be done at the expense of imposing an additional work load on the heart. This latter effect is less marked with glyceryl trinitrate and related compounds than with other coronary dilators. In addition, Zoll and Norman (1952) found sodium nitrite to be the only one of the commonly-used vasodilators capable of encouraging collateral circulation, and the only substance capable of preventing experimental myocardial infarction by coronary occlusion. The work of Lumb and Hardy (1963) referred to previously, demonstrated the capacity of Peritrate to enhance collateral circulation in the pig's heart.

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# 43

# Pharmacologic Agents in Hypertension

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### Incidence and distribution of hypertension.

Hypertension and its sequelae appear to be one of the most frequent causes of death in the United States. Hypertension, at least in a mild form, is very common in middle-aged and old people. In the extensive series of tests by Master *et al.* (1950), blood pressures of 140/90 mm. or higher were found in about 40 per cent of the men and women in the age groups 45 to 49 years. These findings were elevated to 60 per cent in the age group 60 to 64 years. It is estimated that there are between 15 and 18 million cases of hypertension in the United States. Some degree of permanent hypertension occurs in about half of the people in the United States who reach the sixth decade. The average life expectancy now is 70. As the span of life increases further it is to be expected that there will be a greater increase in the incidence of hypertension.

There is undoubtedly an ethnic factor which plays an important role in the blood pressure levels of various races. For example, Africans, Indians, Chinese, Filipinos, and South American Indians have lower blood pressure levels than the white race. In persons of the same age group the difference averages 10 to 20 mm. systolic, and 8 to 15 mm. diastolic. There is also convincing evidence to show that environment is an important factor in the pathogenesis of essential hypertension. Where the average blood pressure levels in a given population are low, there is usually a low incidence of essential hypertension. The influence of environment is illustrated in the case of the African Negro, where hypertension is seldom encountered in their traditional tropical milieu. In America, however, hypertension is approximately 2½ times more common among Negroes than among whites. The data indicate that the cardiovascular system of the Negro is less able to adapt itself to stimuli of environmental and neurogenic origin (Gelfand, 1957).

### Factors in the maintenance of normal blood pressure.

The factors responsible for the maintenance of normal blood pressure are mainly:

1. The pumping action of the heart
2. The peripheral resistance
3. The quantity of blood in the arterial system
4. The viscosity of the blood
5. The elasticity of the arterial walls

The systolic blood pressure is related directly to the cardiac output, while the diastolic level is indicative of the peripheral resistance. It is the diastolic blood pressure which is of grave concern in the treatment of hypertension, as it is indicative of the underlying causative factor of peripheral resistance.

**Normal blood pressure.** Normal blood pressure within the systemic arteries at rest is a figure which is not agreed upon by all clinicians. However, a normal range of blood pressure may be given, but this in turn undergoes certain variations with regard to age, sex, climate, and general psychosomatic make-up of the individual. The systolic blood pressure is given a normal upper limit of 140 to 150 mm., and the diastolic blood pressure has been assigned a value of 90 to 95 mm. (Master *et al.*, 1950).

**Age and blood pressure.** Mean blood pressure readings increase with age in each sex. This applies to the systolic and diastolic pressures. In the male there is a smooth rise of systolic blood pressure with respect to age up to the age of 50 years. After 50 the rise is accelerated. In women the rise of the curve of systolic blood pressure with respect to age is not as uniform; however, after 50 the acceleration of rise occurs. The diastolic blood pressure of both sexes rises with respect to age after the age of 20. These data, which were collected by Master *et al.* (1950), and which include observations on more than 15,000 subjects, are shown in figure 43-1.

**Primary hypertension.** In 1836 Richard Bright observed an association between a kidney disease, which still bears his name, and cardiac hypertrophy. Cardiac hypertrophy has been recognized as a sequel to chronic hypertension. Thus the kidney has long been implicated in the hypertensive process, and nephritis, or cardiovascular-renal disease, was a frequent diagnosis in many cases of hypertension. Especially was this true when abnormal chemical constituents were present in the urine.

It is well known that hypertension may arise without previous kidney damage and that the disease itself may be associated with a large number of other conditions. Indeed for about 90 per cent of the cases of hypertension no demonstrable lesions can be established as the incriminating causes of the high arterial pressure. These are referred to as cases of *primary* or *essential hypertension* and are in contradistinction to a smaller group referred to as cases of secondary hypertension. In the latter group hypertension appears as a manifestation of some other pathologic condition.

**The brain and primary hypertension.** In primary hypertension arteriolar constriction is the prime causative factor. This in turn may be due to one or many biochemical imbalances in the organism. Tension, conflict, and stress are frequently contributing factors. Psychic factors influence the autonomic centers in the hypothalamus and produce autonomic imbalance. The vasoconstrictor center may be stimulated, causing peripheral vasoconstriction. The posterior lobe of the pituitary gland may furnish to the blood an excess of the vasoconstrictor vasopressin. The anterior lobe may secrete to the blood an excess of ACTH, stimulating the adrenal cortex to secrete DOCA-like steroids such as aldosterone (see page 829), causing sodium retention by the kidney. Psychic factors may cause a discharge of norepinephrine from the adrenal medulla, which is a powerful vasoconstrictor. In addition, the brain has been shown to be capable of secreting into the blood a potent vasoconstrictor humoral agent. By these, and perhaps by other more obscure mechanisms, the brain can produce, as a result of unfavorable psychic responses, arteriolar constriction.

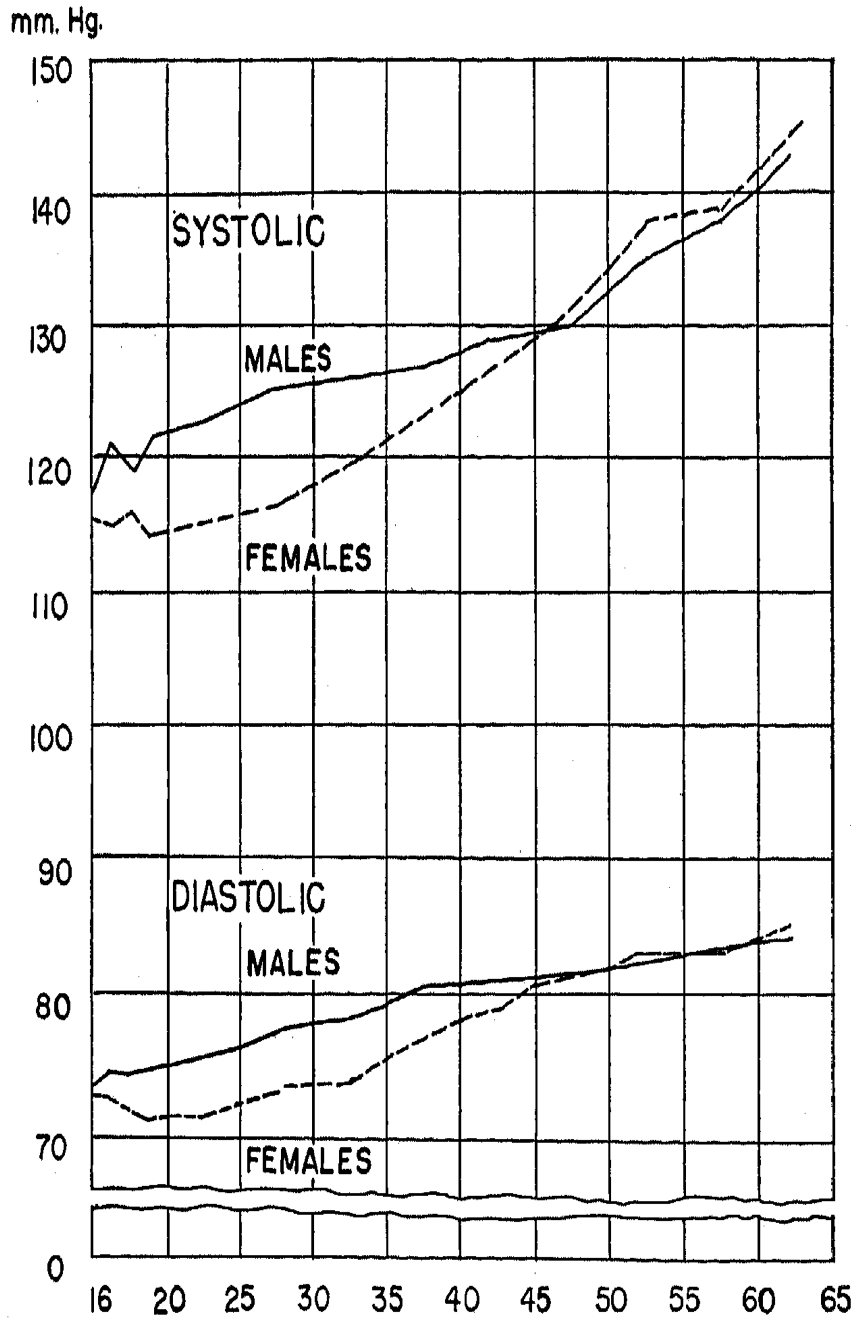


FIG. 43-1. Mean blood pressure readings. (From A. M. Master, L. I. Dublin, and H. H. Marks, J. A. M. A., **143**: 1464, 1950.)

**Renal hypertension.** Tigerstedt and Bergman in 1898 obtained an extract from normal rabbit kidneys which produced an increase in blood pressure when injected into other animals. The most important stride that has been made in this field was the result of the experiments by Goldblatt *et al.* (1934 *et seq.*). These investigators were the first consistently to produce permanent hypertension by partially constricting the renal arteries of dogs.

The literature on experimental renal hypertension is immense, and research has been continuing in this field in an attempt to elucidate the problem of hypertension in man.

It appears that ischemia and perhaps other alterations resulting from a diminished blood supply to the kidneys cause the release into the blood from the kidney a globulin called *"renin."* Renin is a proteolytic enzyme. Renin, as such, is not a pressor substance, but hydrolyzes an *alpha globulin* probably produced in the liver, called *hypertensinogen* or *renin activator.* The product is a polypeptide which is a pressor substance. It is called *angiotonin* or *hypertensin.* The name *angiotensin* has now been chosen for this substance. The relationship between renal hypertension and high blood pressure occurring in human subjects has not been completely elucidated. It is true that often primary kidney disease will cause hypertension, and if unilateral it may be mitigated by the removal of the diseased kidney. However, no significant amounts of renin or angiotensin can be found in the systemic blood of patients with chronic hypertension, although renin is sometimes detectable in patients with hypertension while the blood pressure is still rising. It is of interest that Castleman and Smithwick (1943), in kidneys removed at operation from hypertensive patients, found no vascular changes which were significantly different from those found in kidneys of normotensive individuals.

Bumpus *et al.* (1957) reported the synthesis of angiotensin, which is an octapeptide. Pressor responses in dogs elicited by the synthetic compound were essentially the same as those evoked by naturally-occurring angiotensin. Experiments conducted by these investigators indicate that the site of pressor response of angiotensin is different from that of the usual pressor amines. The pressor response in the pithed cat proves that the central nervous system is not involved in the action of angiotensin. Synthetic angiotensin also evokes a strong oxytocic action, as does the natural product.

**Hypertension and pressor amines.** The vast compilation of data available regarding hypertension in man indicates that the disease is usually one of *psychosomatic origin.* It is postulated that such personality defects as *subnormal assertiveness* and *obsessive-compulsive tendencies* produce *tension* and *conflicts* which the individual fails to resolve. These, acting through the hypothalamus, cause excessive sympathetic discharge. Neurogenic vasoconstriction is produced. The renal vascular bed is included. Renal vasoconstriction, which is not completely compensated by a rise in arterial tension, provokes the kidney to release pressor substances into the blood. These augment the pressor response to the released catecholamines.

Raab (1959) showed that when rats are treated with desoxycortisone acetate (DCA) the pressor response to epinephrine is accentuated. He proposed that the sensitization of the vascular system under such treatment may become more reactive to endogenous catecholamines and thus present the picture of primary hypertension. The same experiments have been repeated in man and confirmed. Evidence appears to be accumulating from many sources that the catecholamines, particularly norepinephrine, are one of the salient etiologic causes of primary hypertension.

Schmiterlöw (1948) identified the presence of norepinephrine in the walls of arteries. Burn and Rand (1958) showed that nicotine, which causes vasoconstriction of the blood vessels in the rabbit's ear, elicits this action because of the release of norepinephrine from the artery wall. It appears that norepinephrine is becoming increasingly incriminated in the etiology of hypertension.

The pressor amine serotonin (see page 494) elaborated by blood platelets and other tissues is also likely to be implicated in the multifaceted etiology of hypertension.

Great progress has been made in attempting to add to the armamentarium of the physician drugs based upon a correction of the basic etiologic factors of hypertension. At present none of these experiments has brought to the clinics a completely suitable drug useful in the treatment of the disease. Nevertheless great strides have been made. The vasodilators of the nitrite-nitrate series used for three-quarters of a century in the treatment of hypertension are seldom used for this purpose today. A survey of current medical writing shows that the principal drugs used today in the treatment of mild to moderate hypertension are the alkaloid reserpine and thiazide diuretics. For severe hypertension the ganglionic blocking agents guanethidine and hydralazine are often the drugs of choice. As each of these compounds is discussed, it will be observed that their finer pharmacologic profiles reveal that their responses are mediated through their effects on endogenous catecholamines.

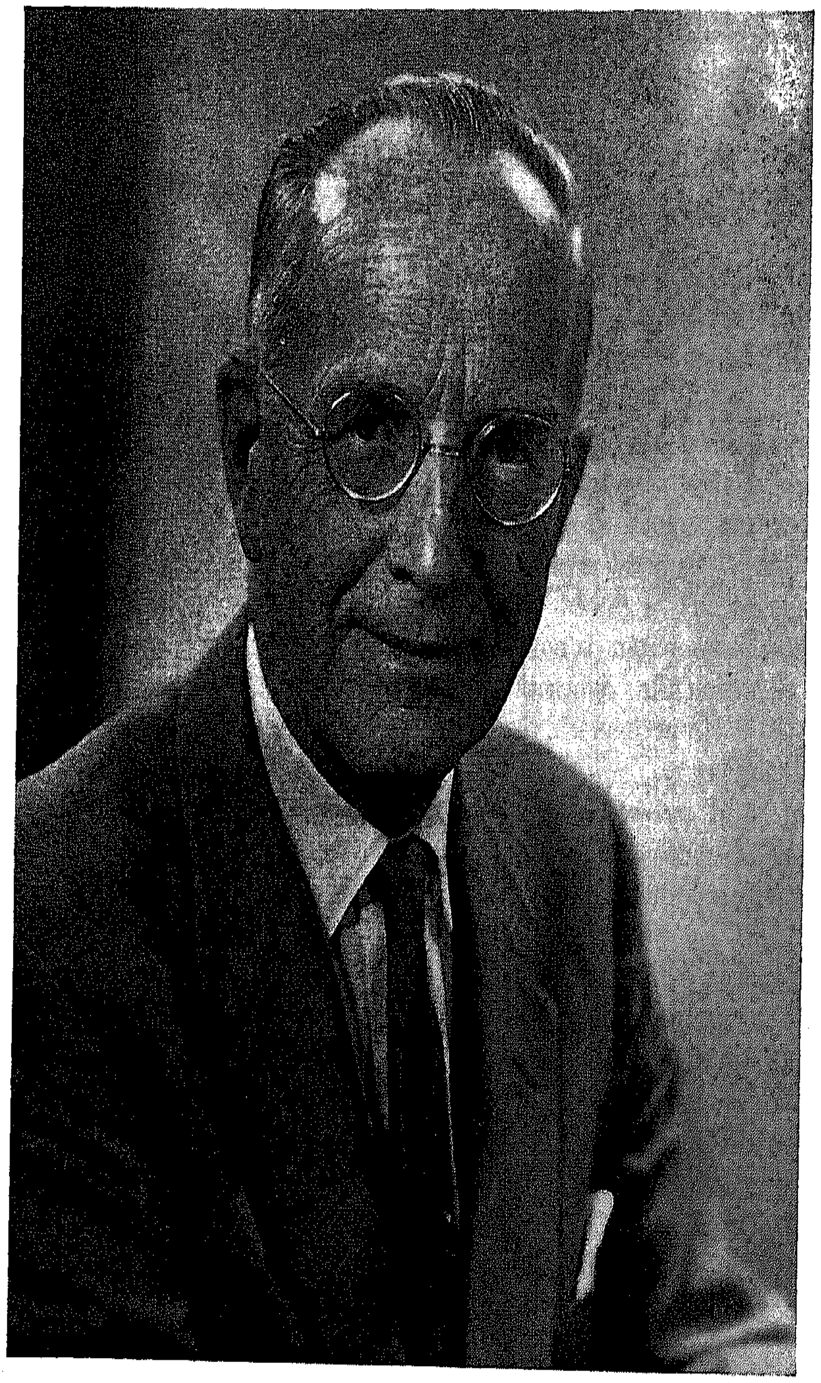
### Rauwolfia in hypertension.

*Rauwolfia serpentina* is a tropical shrub growing widely in India. For centuries the root of the plant has been used in Indian medicine. The powdered root mixed with pepper was employed in the treatment of the insane. Rauwolfia elicits a sedative effect. It was observed that alkaloids obtained from Rauwolfia root elicited hypotensive effects. However, recent interest in Rauwolfia in occidental medicine stems from the work of Vakil (1949), who used the extract in the treatment of hypertension.

**The akaloids of rauwolfia.** Several alkaloids have been isolated from *Rauwolfia serpentina.* Among these are *reserpine, rescinnamine, serpentine, serpentinine, ajmaline, ajmalinine,* and *sarpogenine.*

Since the total alkaloidal content of the root may vary greatly, a careful standardization of whole root preparation is essential. As this is difficult because of the slow action of the drug, it appears preferable to base the therapeutic use on the weight of alkaloids administered.

Reserpine is the most potent agent so far



IRVINE H. PAGE

*Eminent investigator in the field of hypertension*

'Hypertension exemplifies a "disease of regulation" in which the controls of tissue perfusion are set too high; good treatment resets them lower."

isolated and probably accounts for much of the activity of rauwolfia. The total synthesis of reserpine was achieved by Woodward *et al.* (1956). The effect of reserpine can be detected in experimental animals even at a dose of 1 μg./kg. daily given orally for 5 days. Serpentine and ajmaline have no demonstrable effect in doses up to 3 mg./kg.

Reserpine is an ester-alkaloid like the hypotensive veratrum alkaloids. Degradation studies produced evidence to show that reserpine contains the pentacyclic nucleus which is present in the alkaloid yohimbine, as shown on page 575.

**Reserpine, U.S.P.** Reserpine, as recognized by the U. S. Pharmacopeia, is a white or pale buff to slightly yellowish, odorless, crystalline powder. It is insoluble in water and sparingly soluble in alcohol.

The most generally used product of rauwolfia is the alkaloid reserpine. It is available under various trade names such as *Serpasil, Sandril, Serfin, Reserpoid,* and *Raw-Sed.* Rescinnamine is another alkaloid of rauwolfia which is comparable to reserpine in potency and similar to it in its qualitative pharmacologic response (Cronheim *et al.*, 1954).

Syrosingopine (Singoserp) is a derivative of reserpine. Chemically it is carbethoxysyringoyl methylreserpate. It contains a carbethoxy group in place of one of the methyl groups on the benzene ring in the reserpine molecule. It is characterized pharmacologically by being partially devoid of the tranquilizing action of reserpine, but eliciting the cardiovascular effects of the parent alkaloid.

Horita (1958) demonstrated the effect of reserpine on the release of norepinephrine in the cocainized dog. In the anesthetized, cocainized dog, reserpine produces a rise in blood pressure, which is antagonized by adrenergic blocking agents but not by the antiserotonin agent, 2-bromlysergic acid diethylamide. Horita interpreted this observation to indicate that the pressor response was mediated through the release of catecholamines from the tissues by reserpine. In normal animals the amount of pressor amines released is insufficient to exert a pharmacologic response. However, when the adrenergic fibers are sensitized by cocaine, the effect becomes manifest.

Krayer (1958) demonstrated that the cardiac acceleration produced by reserpine in the dog's heart in the heart-lung preparation was due to the release of norepinephrine from the heart. In the failing heart reserpine was shown to evoke a positive inotropic effect. Dogs treated repeatedly with reserpine prior to the experiment were found to have no norepinephrine stores in their cardiac tissues. In these animals reserpine did not elicit an increase in heart rate.

Burn and Rand (1958) showed that the release of norepinephrine from the arterial wall by nicotine was blocked by the ganglionic blocking agent hexamethonium. They propose that the release of norepinephrine caused by a chemical agent or as a response to neuronal stimulation might be an important factor in the etiology of peripheral vascular disease and hypertension. They observed that phenobarbital had some activity in diminishing the release of norepinephrine. When norepinephrine is released from its stores in the arterial wall, the arteries become more sensitive to the pressor response of norepinephrine. Reserpine, in causing the release of norepinephrine from the arterial wall, thus sensitizes the vessels to the response of norepinephrine. Bein (1955) demonstrated that reserpine diminishes the stream of sympathetic impulses from the sympathetic centers which impinge upon the arterial wall. Therefore, although the vascular tone is increased by the release of norepinephrine from the arterial wall, the intensity of the impulses reaching the vessels is less owing to the diminution of central outflow. Burn and Rand very cogently state, "The effect of reserpine on the vascular tone is thus not simple."

**Response of the circulatory system to reserpine.** The action of rauwolfia and its principal alkaloid, reserpine, in the treatment of mental disturbances is discussed on page 500. We shall consider here the activity which is responsible for the use of the drug in the treatment of hypertension.

The principal gross pharmacologic responses to reserpine are *tranquilization, hypotension,* and *bradycardia.* In contrast to most drugs used in the treatment of hypertension, reserpine exhibits a latent period of 1 to 3 days before its complete action becomes manifest. The locus of action of reserpine may be gleaned from an analysis of the various responses elicited in laboratory animals.

1. Reserpine has been shown to evoke no peripheral adrenolytic or parasympathomimetic activity (Plummer *et al.*, 1954).
2. Blockade of transmission in autonomic ganglia is not elicited by reserpine (Bein, 1953).
3. Reserpine produces relaxation of the nictitating membrane, which indicates diminished sympathetic predominance.
4. Reserpine increases gastric secretion and increased gastrointestinal activity. Since it was shown that the drug is devoid of cholinergic activity and peripheral adrenolytic action, this points to an action involving central sympathetic predominance. This action is likely to be mediated at the level of the hypothalamus where autonomic balance is integrated. However, Rider (1955) studied the gastric analyses of 20 patients with various gastrointestinal disorders who were receiving 0.25 mg. of reserpine 4 times daily. No consistent change in volume, free hydrochloric acid concentration, or acid output was observed after prolonged administration of the drug.
5. Furthermore, reserpine affects the temperature regulation of the rabbit and monkey, causing hypothermia. This is probably mediated through its hypothalamic action.
6. Inhibition of hypothalamic sympathetic activity, permitting a predominance of para-

sympathetic influence, elicits sedation, myosis, bradycardia, and relaxation of peripheral blood vessels. These responses follow the administration of reserpine.

7. Trapold *et al.* (1954) produced asphyxial stimulation of the vasomotor center by increased intracranial pressure. The hypertensive response evoked was not effectively combated by reserpine, indicating that the action is likely mediated at a higher level in the brain than the medulla.

These studies indicate that the action of reserpine in producing hypotension is mediated through its *hypothalamic action by diminishing sympathetic predominance.* It appears that the release of norepinephrine by reserpine from the brain, heart, and arterial walls has been established. The problem of fitting the multifaceted central and peripheral effects of reserpine precisely into the matrix of its hypotensive action will require further study.

Other interesting pharmacologic actions of rauwolfia have been observed. For example, Gourzis (1955) found that the alkaloid extract of rauwolfia, when administered to dogs in sedating doses, elevated the threshold to veratrum-induced emesis. Schneider *et al.* (1955), in a study of increased gastric acid secreted in dogs by reserpine, suggest that reserpine, like tetraethyl ammonium bromide, stimulates the parasympathetic ganglia. Schneider (1954) showed that reserpine antagonized morphine analgesia in mice, whereas chlorpromazine prolonged it.

Numerof *et al.* (1955) studied the metabolism of $C^{14}$-labeled reserpine in mice. The alkaloid, whether administered orally or intravenously, is rapidly metabolized; 30 to 40 per cent of the dose appears in the urine within 4 hours as trimethoxybenzoic acid. Fecal excretion of unchanged reserpine constitutes about 8 per cent of an oral dose.

**Therapeutic use of rauwolfia in hypertension.** Wilkins and Judson (1953) published the first extensive report on the use of rauwolfia in hypertensive patients of the less severe labile type. They observed that 30 to 50 per cent of these patients reacted favorably subjectively and objectively to the treatment. Hypertension of nervous origin with tachycardia responded best to the action of rauwolfia. Severe hypertensives with renal insufficiency did not respond well to the treatment with rauwolfia alone. However, the sedative action of the drug appeared beneficial.

The drug reduces systolic and diastolic blood pressures in those individuals where it is effective. In most cases this is accompanied by a bradycardia. The patients frequently experience a sense of well-being and relaxation.

The findings of these investigators have been confirmed in many clinics. The literature is replete with accounts of rauwolfia and reserpine in the treatment of hypertension.

From the data extant it is apparent that reserpine is valuable in the treatment of mild, labile types of hypertension of neurogenic origin. For the moderate and more severe grades of the disease, it is necessary to use the drug in conjunction with other more potent drugs such as the ganglionic blocking agents or hydralazine.

The side effects of reserpine therapy frequently encountered are *nasal stuffiness, diarrhea, drowsiness, disturbed sleep,* and *dizziness.* Many patients become tolerant to these effects, which are minimized upon continued treatment. Of dire concern, however, are the states of depression which may be caused by reserpine. Freis (1954) described 5 cases of depression from reserpine therapy. He advised low dosage schedules to minimize this possibility. Kass and Brown (1955), who recorded a number of depressed states following reserpine therapy, point out the interdiction of the drug in "borderline" patients who are experiencing difficulty in maintaining a marginal emotional adjustment. Daily dosage schedules may be increased to 2.5 mg.; however, the danger of mental symptoms must always be considered.

Rauwolfia is available as Raudixin, containing 50 mg. of the whole root of *Rauwolfia serpentina;* also as Rawiloid, containing 2 mg. of the active alkaloidal extract, and reserpine, containing 0.25 mg. per tablet. Usually 2 or 3 tablets are given daily until the desired effect is achieved; then the dose is reduced. When required, the drug may be given parenterally.

Some clinicians prefer the whole root of rauwolfia or an extract of the root containing all of the alkaloids. In these preparations, in addition to reserpine there is the alkaloid rescinnamine (Resamine), which is only slightly less potent than reserpine as a hypotensive agent but is said to be less prone to produce excessive sedation and mental depression. The dose of rescinnamine in the treatment of hypertension is 0.25 to 1 mg. daily. Cronheim *et al.* (1957) demonstrated a potentiating effect of alkaloidal mixtures of reserpine plus rescinnamine. It does appear that advantage might be achieved in therapy with rauwolfia extracts, as it has been shown that the hypotensive potency of Rawiloid in dogs is greater than can be accounted for by its reserpine content.

**Syrosingopine (Singoserp).** Singoserp is not a naturally-occurring alkaloid in the plant rauwolfia. It is a synthetic derivative of the alkaloid reserpine. Chemically it is carbethoxysyringoyl methylreserpate (see page 682). This compound is the outcome of an extensive chemical and pharmacologic study of the molecule of reserpine, aimed at obtaining a compound with hypotensive activity and devoid of the tranquilizing action of reserpine.

*Pharmacologic response.* Singoserp elicits quantitatively and qualitatively the same type of hypotensive response and cardiac slowing as does reserpine. Upon the central nervous system, Singoserp exerts a mild calming effect. That its action is less marked than that of reserpine is shown by the fact that the dose of Singoserp required to eliminate behavorial expression of fear and anxiety in conditioned rats subjected to stress is 40 times greater than that of reserpine (Plummer *et al.*, 1959).

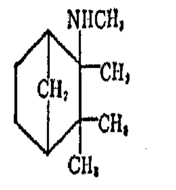
The mechanism by which Singoserp lowers the blood pressure has been investigated by Plummer *et al.* (1959). They agree that the action of Singoserp is primarily peripheral, whereas the action of reserpine is both central and peripheral. The principal peripheral action of Singoserp, according to these investigators, is as follows. It causes an inhibition of the flow of sympathetic impulses to the arteries by depleting the mediating neurohormone norepinephrine from nerve endings. The second effect is suggested as a central action, increasing parasympathetic activity by the releasing of serotonin in the brain. Singoserp appears to have little or no capacity to release norepinephrine in the brain. In laboratory animals, Singoserp will cause a depressor response and bradycardia without producing "overt sedation."

*Clinical application.* The synthesis of Singoserp represents an advance in the therapy of hypertension. It appears to eliminate the principal objection to reserpine therapy in hypertension, *i.e.*, depression and behavioral changes of an undesirable character. Extensive clinical trials have confirmed the pharmacologic studies, although the hypotensive effect appears to be weaker than that of reserpine. The dosage schedule of Singoserp in hypertension is similar to that recommended for reserpine. In milder cases of hypertension 0.25 mg. 3 or 4 times a·day is adequate (Wolffe, 1958). In more severe cases 1 mg. 4 times a day is well tolerated (Calesnick, 1959). Certain observers found that a larger dose of Singoserp was required for hypertensive therapy than was necessary with reserpine, although with the larger dosage schedule nasal stuffiness was not encountered. Consonant with these observations are the studies of Herrmann *et al.* (1959), who treated 77 ambulant patients with essential hypertension with Singoserp. They found it necessary to use a higher dosage schedule than that required for reserpine. However, side effects were infrequent, and their success in the management of hypertension appeared to be tantamount to that achieved with reserpine.

### Ganglionic blocking agents.

There are a number of chemical compounds which elicit autonomic ganglionic blockade. Owing to the blockade of the sympathetic ganglia which are motor to the arteries, these agents evoke a marked hypotensive response. The first of these compounds to acquire general acceptance as a hypotensive agent was hexamethonium chloride. Owing to poor gastrointestinal absorption and many disconcerting side effects this drug was replaced by *pentolinium tartrate,* which offered certain advantages. Other ganglionic blocking agents used in hypertension are *chlorisondamine* and *trimethidinium.* All of these agents appear to be inferior to *Mecamylamine, U.S.P.*, which will be discussed in detail. For a description and use of the other antihypertensive ganglionic blocking agents, see Chapter 43 of the 5th edition.

**Mecamylamine, U.S.P. (Inversine).** Mecamylamine is a different type of ganglionic blocking agent. Mecamylamine contains no quaternary nitrogen atoms in the molecule. It is a secondary amine, as shown in the formula.



Mecamylamine, U.S.P.
Inversine
(N,2,3,3-tetramethyl-2-norcamphanamine)

Mecamylamine is a white, crystalline powder which is soluble in water.

*Pharmacologic response.* Moyer *et al.* (1955) found that mecamylamine is absorbed completely from the gastrointestinal tract. In this respect it differs from the quaternary nitrogen ganglionic blocking agents, which are only partially absorbed. The activity of mecamylamine as a ganglionic blocking agent has been shown to be 3 to 4 times more persistent than that produced by Ansolysen. Mecamylamine elicits a mild curare-like action on skeletal muscle. When measured in laboratory animals the curare action was found to be 0.08 of that evoked by *d*-tubocurarine. Mecamylamine prolongs the sleeping time of mice induced by barbiturates in a manner similar to reserpine. Sympathomimetic drugs reverse the hypotensive effect induced by mecamylamine. Extensive pharmacologic studies by Stone *et al.* (1956) demonstrated that mecamylamine "possesses ganglionic blocking properties characterized by a high order of potency, specificity, and a long duration of action."

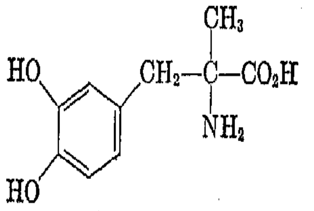
*Therapeutic use.* This chemically different type of ganglionic blocking agent is indicated in the treatment of moderately severe, severe, and malignant types of hypertension. Moyer *et al.* (1955) studied mecamylamine critically in a series of hypertensive patients and compared its efficacy with that of hexamethonium and Ansolysen. All patients were given 0.25 mg. of reserpine 4 times daily. Fifty patients who received in addition a 17-mg. daily dose of mecamylamine were followed for 7 weeks. Of this group 92 per cent responded to treatment. In 75 patients who received a daily dose of 2307 mg. of hexamethonium, 76 per cent responded. In 75 patients with a daily dose of 341 mg. of Ansolysen, 79 per cent responded. There appeared to be more sedation in the mecamylamine group than in the 2 other groups. *Constipation* and *weakness* were frequent findings. However, blurring of vision occurred in only 8 of the 50 patients treated with mecamylamine.

Freis and Wilson (1956) found mecamylamine to be a useful drug in the treatment of a series of moderately severe hypertensive patients. Continuous therapy for 1 to 4 months frequently resulted in the improvement of the appearance of the optic fundi and occasionally in the electrocardiographic patterns. Sellers and Mitchell (1956) employed mecamylamine in 20 severe hypertensive patients at a dosage level of 7.5 to 17.5 mg. daily. Reserpine, 1 mg. daily, was added to the regimen of 17 of the 20 patients. All but one patient tolerated the therapy well; 16 of the group experienced constipation; 3 patients experienced blurred vision and xerostomia. They state: "Because of almost complete absorption from the gut, mecamylamine allows more predictable dose-effect relationship than do other similar agents which have been used in the treatment of hypertension."

From the available clinical literature the evidence is strikingly suggestive that mecamylamine represents a distinct advance in the treatment of hypertension with autonomic ganglionic blocking agents. Despite the improvement in this type of therapy over the last decade, the use of ganglionic blocking agents is fraught with many untoward side effects. Wilkins (1957) states: "I am inclined to postpone the use of ganglionic-blocking agents as a last resort when treating patients with hypertension of the ordinary benign, non-progressive sort. Even in malignant hypertension, they are reserved for only the most urgent and resistant phases of the syndrome."

### Methyldopa (Aldomet).

Methyldopa is another drug useful in the treatment of mild to moderately severe primary hypertension. Its structure is shown in the formula:



Methyldopa
Aldomet
[*l*-3-(3,4-dihydroxyphenyl)-2-methylalanine]

**Pharmacologic response and mechanism of action.** The proposed mechanism of action for methyldopa in the treatment of hypertension is that it blocks the synthesis of norepinephrine. The decarboxylation of "dopa" is a step in the enzymic synthesis of the pressor amine. Methyldopa is a decarboxylase inhibitor and depresses the conversion of "dopa" to dopamine, essential for the formation of norepinephrine. In addition, the compound inhibits the conversion of 5-hydroxytryptophan to its amine serotonin. In laboratory animals, the administration of methyldopa evokes a net reduction in the tissue levels of norepinephrine, epinephrine, and serotonin. The degree of reduction varies in different tissues. The inhibition of the synthesis of the catecholamines and serotonin is reversible. At excessively high dosage levels, paralysis of sympathetic control does not occur.

Methyldopa is well absorbed from the gastrointestinal tract and evokes no direct deleterious effect upon renal or cardiac functions. Chronic feeding studies in various laboratory animals at high dosage levels revealed no histopathologic or hematologic changes deemed to be clinically significant.

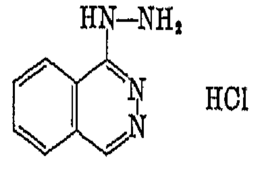
**Clinical studies with methyldopa.** The majority of clinical studies with methyldopa in the treatment of hypertension is favorable. It appears to be more effective in primary hypertension than in the cases presenting renal involvement. The reduction of blood pressure evoked by methyldopa, similar to that of other antihypertensive drugs, is more pronounced when standing than when the patient is supine. It is doubtful whether methyldopa evokes a significant reduction in peripheral arteriolar resistance. The depressor response is likely to stem from a decrease in cardiac output.

Gillespie *et al.* (1962), in a carefully controlled study with 52 hypertensive patients, found methyldopa to be an effective agent with advantages over other antihypertensive drugs. The advantages cited were effectiveness in all degrees of hypertension, smoothness of effect, and its tranquilizing action. Not all observers agree with this enthusiastic report; thus Dollery and Harrington (1962) used the drug in 59 patients for periods up to 1 year. In ⅓ of the patients treatment was abandoned because of its ineffectiveness. It appears that the most satisfactory results are obtained when methyldopa is used simultaneously with thiazide therapy. Wilson *et al.* (1963) observed that the combination was more effective than the use of either drug alone. Of interest is the observation that methyldopa alone produces slight increases in body weight that were not encountered with the combination. The combination of drugs is available under the name of Aldoril-25, containing 250 mg. of methyldopa and 25 mg. of hydrochlorothiazide.

The side effects of methyldopa are *sedation* and occasionally *psychic depression.* In addition, *xerostomia, gastrointestinal distress, edema, changes in liver function tests, dizziness,* and *lightheadedness* are encountered. On rare occasions *impotence, arthralgia,* and *reversible reduction of the white blood cell count* have been reported. Evidence indicates excretion of the unaltered compound by the kidney in the urine. We agree with most clinical investigators that this drug represents a useful adjunct to antihypertensive therapy and that it is certainly a novel approach. Although from the discussion it is clear that it is not the ideal antihypertensive agent, it bids fair to be valuable in the treatment of a segment of hypertensive patients.

### Hydralazine Hydrochloride (Apresoline).

Hydralazine is used as a valuable adjunct in the treatment of hypertension. Its structure is shown in the formula below:



Hydralazine Hydrochloride
Apresoline
(1-hydrazinophthalazine)

Hydralazine is used as its hydrochloride. The salt is a pale yellow to white, crystalline powder. It is soluble in water.

**Pharmacologic response.** This compound as a pharmacologic agent is unique from the point of view of its chemical structure. Its value in hypertension is dependent upon several components of its pharmacologic action. Its principal effect is central; however, this involves no sedative component. Hydralazine exhibits a mild degree of adrenergic blocking. It will diminish the hypertensive response to the catecholamines. Centrally its locus of action is apparently in the midbrain. Here it diminishes the outflow of sympathetic vasopressor discharges.

Hydralazine has been shown to inhibit or block the pressor responses elicited by *angiotonin, serotonin,* and *pherentasin.* The cerebral humoral vasopressor substance is also effectively inhibited by hydralazine.

Hydralazine has been shown to cause coronary artery dilatation in high dilution in the isolated rabbit's heart. A most striking effect of hydralazine is its capacity to increase renal blood flow during the hypotensive phase of its action. Moyer *et al.* (1951) observed this effect in trained unanesthetized dogs; in certain animals the renal blood flow increased 100 per cent.

Hafkenschiel (1952) observed that the oral administration of 10 to 20 mg. of hydralazine caused a "significant relaxation of cerebral vascular tone." This occurred without reducing cerebral blood flow. The tests were conducted on hypertensive patients.

**Use in hypertension.** Hydralazine has enjoyed wide use in the treatment of hypertension. The compound has produced successful reduction of blood pressure in many cases; in others its effect has been disappointing. The principal application of hydralazine appears to be in combination with reserpine, when the latter drug fails to evoke a sufficiently significant depressor response.

Page (1951) studied the effects of hydralazine in 70 patients with essential hypertension and also the malignant form of the disease. Of the group, 5 could not tolerate the drug. About ½ of the group experienced a fall in diastolic blood pressure of 20 mm. or more; 14 had a questionable fall of 14 mm., and 17 of the individuals experienced no effect. The dosage ranged from 100 mg. to 1400 mg. daily. He observed that in certain individuals the malignant syndrome appeared to be reversed. Marked orthostatic hypotension often occurred after initial treatment. Headache was produced by the use of the drug in the early stages but later disappeared. Nausea and vomiting was experienced by 18 per cent of the patients from the administration of the drug.

Schroeder (1952) studied 50 hypertensives taking hydralazine for 1 to 40 weeks. Significant lowering of the diastolic blood pressure by 20 mm. or more occurred in 35 cases. However, in only a few were the normotensive levels maintained. He observed no deleterious effects upon the kidneys or heart. He states that the agent represents a true antihypertensive drug of moderate potency.

Johnson *et al.* (1952) used hydralazine in 16 hypertensive patients. A dosage schedule of 50 to 150 mg. a day reduced the systolic blood pressure in 12 of the patients by 20 mm. or more. Postural hypotension occurred in 15 of the cases. Attempts to achieve a greater reduction in blood pressure for longer periods resulted in the development of tolerance to the drug. Side effects were also encountered. Among these were *headache, dizziness, tachycardia, palpitation,* and *nausea.*

Blood dyscrasias are possible as the result of hydralazine therapy. Kaufman (1953) reported a case of *pancytopenia* in a woman 44 years old following a 7-month course of hydralazine therapy. Hematologic improvement followed the discontinuance of the drug. Morrow *et al.* (1953) encountered 6 cases of drug fever and 16 cases of a drug-induced arthritic syndrome among 250 hypertensives treated with hydralazine-hexamethonium therapy. Five of the series died of interstitial pneumonia.

It is evident that hydralazine therapy, combined with other hypotensive agents, principally reserpine, achieves the most satisfactory results.

The data clearly indicate that hydralazine can serve a very useful purpose in the treatment of hypertension. Its field of usefulness appears to be limited. In addition, the seriousness of the side effects encountered is a distinct disadvantage of hydralazine therapy.

Moser and Mattingly (1955) summarize their evaluation of the use of hydralazine in hypertension as follows: (1) its use is not justified in early cases of labile hypertension; (2) in moderately severe hypertension, when used without other supportive therapy, it is seldom effective in producing significant lowering of the blood pressure; (3) in severe hypertension it may be valuable with ganglionic blocking agents or reserpine for the purpose of rapidly reducing the blood pressure.

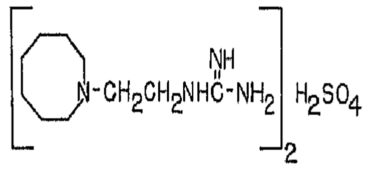
Since hypertension is caused by many different factors, combination drug therapy is frequently better than a single drug. Thus some patients respond well to the ganglionic blocking agents. Others respond better to hydralazine, and still others to a combination of the drugs.

Hydralazine is also recommended for use in the treatment of the toxemias of pregnancy (Assali *et al.*, 1953). Vasoconstriction in the pregnant hypertensive is probably mediated through humoral substances such as pherentasin and angiotensin resulting from renal ischemia. Through its central and peripheral actions, hydralazine opposes the action of these humoral agents. For this purpose hydralazine may be given by the usual oral route, or in critical cases 20 mg. may be administered intravenously.

### Guanethidine (Ismelin).

Guanethidine represents an entirely new type of chemical structure evoking unique pharmacologic properties. The structure of guanethidine

is shown in the formula:



Guanethidine
[2-(octahydro-1-azocinyl)-ethyl]-
guanidine sulfate

Guanethidine is a white, crystalline powder which is soluble in water.

**Pharmacologic response.** Maxwell *et al.* (1960) studied the pharmacologic responses to guanethidine. They concluded that the prolonged hypotensive response is due to its chronically interfering with the release and/or distribution of the neurohumoral transmitter at the sympathetic neuromuscular junction. Subsequent studies demonstrated that guanethidine caused the release of norepinephrine from the heart and spleen. Abboud and Eckstein (1962) observed that guanethidine caused vasodilatation by direct action on vascular smooth musculature. The action became more pronounced after depletion of the catecholamines by reserpine and repeated administration of guanethidine. They suggest that the action may stem, at least in part, from the stimulation of adrenergic dilator receptors.

Guanethidine markedly lowered the blood pressure in neurogenic and renal hypertensive dogs. Its effect was slight in normotensive dogs. Guanethidine antagonized the hypertensive action of amphetamine and the pressor response to bilateral occlusion of the carotid arteries. The duration of these responses was from 4 days to 3 weeks following a single intravenous injection. The preliminary response to the drug is one resembling sympathetic stimulation and lasting about 3 hours. Guanethidine was shown to evoke only a transient autonomic ganglionic blocking action. Of special interest was the observation that during the period of sympathetic atony evoked by guanethidine, the nictitating membranes were hyper-responsive to injected norepinephrine.

For 10 to 30 minutes after the intravenous injection of 15 mg./kg. of guanethidine into dogs, there occurred panting, piloerection, occasional emesis, and diarrhea. The diarrhea persisted for about 24 hours. There were no gross or microscopic abnormalities in the principal organs of dogs following 20 to 40 mg./kg. of guanethidine orally each day over a 30-day period. The oral $LD_{50}$ in rats was approximately 1000 mg./kg.

**Therapeutic use.** Guanethidine had therapeutic trial in the treatment of hypertension (Page and Dustan, 1959; Frohlich and Freis, 1959; and Richardson and Wyso, 1959). Each of these investigators observed a marked hypotensive effect evoked by guanethidine in moderately severe and severe hypertensive patients. Its use at present as an antihypertensive drug is extensive. The average daily maintenance dose of guanethidine in ambulatory patients was found to lie between 10 and 25 mg. The initial dose is kept minimal until a blood pressure fall is noted, and then the dose is reduced to the lowest effective level. In hospitalized patients an initial oral dose of 50 mg. is recommended and followed by 25 mg. 3 times daily until effective lowering of the blood pressure occurs. Then the dose of guanethidine is adjusted upward or downward as indicated. Guanethidine is available in 10- and 25-mg. tablets. It is also used parenterally when a rapid hypotensive action is desired.

Brest *et al.* (1960) found guanethidine effective in 12 carefully selected hypertensive patients. Significant postural hypotensive responses were evoked in 7 of the patients who received oral medication. The intravenous injection of guanethidine produced hypotensive responses that endured for 48 hours or longer. They found the incidence of side effects minimal and encountered no toxic reactions.

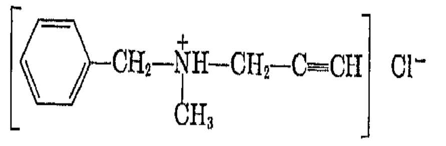
The side effects with guanethidine are postural hypotension, light headedness, and dizziness. While guanethidine is not an autonomic ganglionic blocking agent, it appears to be equally as potent as a hypotensive agent. Guanethidine did not produce impotence; however, ejaculation was inhibited in some patients. Diarrhea was an annoying symptom in some patients, and certain ambulatory patients experienced fatiguability.

Many subsequent studies have shown the value of guanethidine in the treatment of hypertension. After a normotensive state is achieved, many patients may be controlled with a single daily dose. The side effects are not severe and may be controlled or obviated by careful titration of the patient's response. The drug is especially useful in elevated diastolic blood pressure (Brest and Moyer, 1962).

**Bretylium** is an English antihypertensive drug with a brominated benzyl quaternary amine structure. Like guanethidine, bretylium diminishes the activity of the sympathetic nervous system and evokes hypotension. Evidence suggests that bretylium accumulates in adrenergic nerves and blocks transmission of the impulses through them. The hypotensive response to bretylium is of shorter duration than that of guanethidine.

**Pargyline Hydrochloride (Eutonyl).**

Pargyline is a monoamine oxidase inhibitor that does not contain a hydrazine ring structure. Like other MAO inhibitors it evokes hypotension, and the compound is used mainly as an antihypertensive agent. The structure of pargyline is shown in the formula.



It occurs as a white, crystalline powder that is freely soluble in water.

**Pharmacologic response.** In laboratory animals pargyline is well absorbed upon intraperitoneal administration and partially absorbed when given by mouth. It is excreted mostly unaltered in the urine. The oral acute toxicity is low: for rats the $LD_{50}$ is 250 mg./kg. Fatal doses evoke extreme stimulation, collapse, and terminal hyperthermia. Chronic feeding studies in 3 species of animals revealed no specific organ toxicity and indicated the drug's availability for use in man at the recommended dosage level.

Pargyline is a potent MAO inhibitor *in vitro* and *in vivo*. Its potency is equal to that of nialamide. The drug increases the catecholamine levels in the brain and will reverse the depression elicited by reserpine. Costa and Brodie (1961) observed autonomic ganglionic blockade in animals sequential to large doses of pargyline. They suggest that this may be due to the accumulation of norepinephrine in the sympathetic ganglia and may be a facet of its vascular response.

**Clinical use.** Pargyline has found application in the treatment of hypertension of a moderate to severe degree. The drug does not evoke sedation or drowsiness, as do most antihypertensive drugs; on the other hand, it serves as a cerebral antidepressant.

Several reports of the clinical use of pargyline appear in the literature. For example, Bryant *et al.* (1961) used the drug on 38 hypertensive patients in a critical study. A segment of the group (21) had been previously treated with other antihypertensive drugs. Of the 38 patients studied, 31 experienced a clinically significant fall in blood pressure. Of this latter group, 18 became normotensive in the standing and recumbent positions; 5 were normotensive only in the standing position. Besides, 8 patients experienced a mean depressor response of 20 mm. Hg. The study extended over an average of 159 days. In the group that responded well to pargyline, normal blood pressure was difficult to maintain and dosage levels had to be increased. Of the same group, 14 patients suffered side effects.

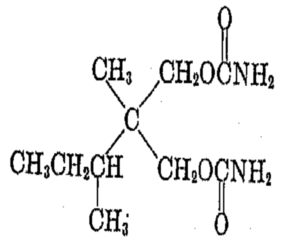
Similar observations were subsequently reported by several groups of investigators. They appear in summary as follows: pargyline is an antihypertensive drug effective in $\frac{1}{3}$ to $\frac{1}{2}$ of the patients to whom it is given. The onset of the hypotensive response is slow, and once the optimal effect is achieved it may be difficult to maintain with a dosage level that does not evoke side effects.

The side effects of pargyline that occur in a segment of the patients can often be prevented or obliterated by carefully controlling or reducing dosage. These are *orthostatic hypotension, weakness, dizziness, faintness,* and *palpitation.* Less frequently encountered untoward effects are *constipation, nausea, vomiting, insomnia, urinary frequency, sweating, xerostomia, nightmares,* and *headache. Impotence* and *delayed ejaculation* have also been reported. Weight gain owing to water retention may occur. This is readily controlled by the simultaneous use of a thiazide diuretic.

The dosage recommended is 25 to 50 mg. for 2 weeks and 35 to 75 mg. for the next 2 weeks. As much as 100 to 250 mg. daily have been given to maintain the normotensive state. Pargyline is supplied in 10-, 25-, and 50-mg. tablets.

**Mebutamate (Capla).**

Mebutamate is a drug closely related chemically to meprobamate. It is used in the treatment of mild hypertension. The structure is shown in the formula:



Mebutamate
Capla
(2-methyl-2-*sec*-butyl-1,3-propandiol dicarbamate)

It occurs as a white, crystalline powder that is sparingly soluble in water.

**Pharmacologic response.** Mebutamate, similar to meprobamate, evokes no effect upon the autonomic nervous system. Its hypotensive action results from a direct depressant effect upon the brain stem vasomotor centers reducing vascular peripheral resistance. The degree of depressor response varies directly with the blood level of the drug.

The acute toxicity of mebutamate is low; the $LD_{50}$ for rats orally is 1160 mg./kg. Chronic toxicity studies with mebutamate at high dosage levels revealed no specific tissue toxicity.

**Clinical use.** The clinical reports of the effectiveness of mebutamate in hypertension are varied. Turek (1961) found it useful in reducing the blood pressure in 39 of 40 cases who had been unresponsive to other therapy. Mild drowsiness in 2 patients was the only side effect. On the other hand, Duarte *et al.* (1960) used mebutamate on 20 hypertensive patients and obtained satisfactory reduction in blood pressure in only 6 of the group. The dose was varied up to 1200 mg. daily in some patients. *Drowsiness, headache, xerostomia, nasal congestion, constipation,* and *orthostatic weakness* occurred in 10 to 20 per cent of the patients at the higher dosage levels.

Corcoran and Loyke (1962) found the drug valuable in moderately severe and some severe cases of hypertension. Their 34 patients were studied for a year on a daily dosage level of 600 to 1200 mg. The effectiveness was enhanced by hydrochlorothiazide. Drowsiness appeared to be the only untoward effect. As one would expect, the antihypertensive action is enhanced by adjunct therapy with hydrochlorothiazide. We are of the opinion that mebutamate may be successfully used in a segment of hypertensive patients with mild elevations in blood pressure, especially where anxiety appears to be a causative factor.

**Diuretic therapy in hypertension.**

For years it has been known that a reduction of the sodium chloride intake of patients with hypertension effected moderate falls in the blood pressure, hence the rationale of the diet of salt restriction in the treatment of hypertension. It has also been established that the status of the electrolyte and water balance of the patient with hypertension markedly affects his responsiveness to hypotensive agents, particularly the ganglionic blocking agents. The accumulation of sodium and water in the tissues appears to affect adversely the efficiency of hypotensive drugs. On the other hand, when the patient is subjected to the action of a diuretic, which produces partial depletion of body fluid and sodium, there is generally a marked sensitivity to hypotensive drugs. With the mild diuretic drugs of the xanthine series such as theophylline, this effect is not readily apparent. With the advent of *chlorothiazide* (see page 797), eliciting potent diuretic and saluretic properties for sodium chloride, another valuable agent has been added to the armamentarium of hypotensive drugs.

In addition to the effect of the thiazides in producing a loss of sodium and chloride ions which, in turn, affects the gradient of sodium ions between the intracellular and extracellular spaces, they appear to evoke vasodilatation directly. Whether this effect is direct on the arterial musculature or mediated through catecholamine release has not been definitely established. Preziosi *et al.* (1961) observed that in dogs and mice high levels of hydrochlorothiazide elicited "adrenolytic," "sympatholytic," and direct "myolytic" properties. They consider this a facet of their vascular inhibitory action. In our opinion, the principal effect of the thiazide diuretics in hypertension is due to their natriuretic action.

It has been established that chlorothiazide and its newer derivatives alone will evoke a hypotensive response in a large segment of hypertensive patients. The hypotensive effect is most pronounced in those patients with a distorted electrolyte balance accompanied by the abnormal retention of water. When hypotensive drugs such as reserpine or the autonomic ganglionic blocking agents are used in the treatment of hypertension, the concomitant use of a thiazide diuretic synergizes the hypotensive response. Thus it makes possible the achievement of adequate hypotensive response with a lower dosage level of the hypotensive agent. Frequently this enables the patient to remain free of untoward side effects which would have been encountered at higher dosage levels. Available for such therapy is *Hydropress-25,* containing in 1 tablet 0.125 mg. of reserpine and 25 mg. of hydrochlorothiazide, and *Hydropress-50,* containing the same quantity of reserpine and 50 mg. of the diuretic agent. The dosage schedule recommended for Hydropress-25 is from 1 to 4 tablets daily and of Hydropress-50, 1 to 2 tablets daily.

**Veratrum.**

The extractive preparations of veratrum are as old as the history of medicine. They were mentioned several times in the writings of Hippocrates. The active principles are alkaloids. The veratrum plants belong to the Liliaceae. The 3 species which have been most investigated in regard to their chemistry are the North American *Veratrum viride*, the European *Veratrum album*, and the Caribbean and Mexican *Schoenocaulon officinale*.

Interest in the extractive preparations of veratrum waned during the twentieth century. Until about 1945 veratrum preparations were used to a limited extent in eclampsia and hypertension. Their use was empiric. The revival of an interest in the veratrum alkaloids stems from the investigations of Krayer *et al.* (1942 *et seq.*) These workers extensively investigated the action of individual alkaloids of the plants, and they laid a sound pharmacologic basis for their therapeutic trial.

The alkaloids of special interest in veratrum because of their hypotensive action are the ester alkaloids Protoveratrine A and B.

These alkaloids are used to a limited extent in the treatment of hypertension. Krayer and Acheson (1946) expressed the view that the vasodepressor response to small doses of these alkaloids is a "vasodilatation of reflex nature." Some of the afferent pathways were found to run in the vagus nerves and none in the aortic nerves and in the sympathetic outflow of the autonomic nervous system. The cardiodecelerator effect is likewise reflex in nature. The afferent fibers appear to have a course similar to those subserving the vasodepressor effect. Thus the prime components of the fall in blood pressure evoked by the veratrum alkaloids are a reflex vasodepressor response and a reflex bradycardia; together those comprise the cardiovascular facets of the "Bezold effect."

The intravenous dose of Protoveratrine A and B is 1.5 to 1.9 $\mu$g./kg., given slowly; the intramuscular or subcutaneous dose is 4 to 6 $\mu$g./kg. On oral administration 1.0 to 2.5 mg. daily in divided doses is effective in lowering the blood pressure in about ⅓ of the patients with hypertension. Unless dosage is regulated carefully, toxic effects such as *nausea, vomiting, hiccup, severe hypotension, bradycardia*, or even *heart block* appear. Atropine sulfate effectively prevents or abolishes bradycardia and heart block. Ephedrine sulfate, 25 to 45 mg. intramuscularly, or other vasoconstrictor agents such as norepinephrine can be used to overcome excessive hypotension.

The protoveratrines also are used in the treatment of hypertension in conjunction with reserpine. The advantage of the combined therapy appears to stem from the lower dosage schedule of the veratrines, the smaller number of toxic side reactions, and the sedative effect of reserpine.

Owing to the narrow margin of safety between the effective hypotensive dose and the dose eliciting disconcerting side effects, the use of veratrum preparations in the treatment of hypertension has waned. For a more complete discussion of the chemistry and pharmacology of veratrum see page 942 of the 4th edition of this text.

### Summary of the status of drugs in hypertension.

Not all hypertensives should be treated with drugs. This statement applies to mild cases of hypertension which are uncomplicated. Reassurance on the part of the physician, rest, tranquility of mind, and mild sedation with phenobarbital, 30 mg. 3 to 4 times daily, are measures which can be employed without disconcerting side effects on the patient. Therapy with other drugs should always be considered in the light of the expected prognosis of the patient who is not treated. For patients with a more severe degree of hypertension, rauwolfia should be considered. If symptomatic relief and a reduction in blood pressure are not achieved, rauwolfia and the diuretic hydrochlorothiazide may be effective. In other cases combination therapy of guanethidine and a thiazide may achieve better results. In severe hypertension rauwolfia and an autonomic ganglionic blocking agent may be considered as the combination therapy that is likely to achieve the best results.

Guanethidine appears to be useful in reducing the diastolic pressure. Often hydralazine also will achieve this end where other agents fail. In addition, the antihypertensive agents methyldopa, pargyline, and mebutamate are available.

In this multifaceted disease, combination therapy is frequently more successful than any single drug. One should also weigh the manometric success achieved against the well-being of the patient under therapy. Drug therapy in severe hypertension has prolonged life, diminished cardiovascular-renal accidents, and caused the regression of the basic disease process. In most cases

side effects are observed. With the antihypertensive agents available, high blood pressure can be reduced in most patients. However, the therapy in severe cases is fraught with side effects which must be endured.

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# 44

# *Pharmacologic Agents Affecting the Clotting Time of Blood*

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The clotting of blood may be influenced by various drugs. Often the action is due to an idiosyncrasy, but certain drugs are employed specifically to alter coagulation in order to achieve a therapeutic effect. Two examples are heparin and bishydroxycoumarin.

## The clotting of blood.

The reactions that effect the clotting of blood are exceedingly complex, but as a guide, a simple scheme is formulated which incorporates the primary clotting factors as well as the probable sequence of their interaction.

The clotting mechanism may be divided into 4 major steps (fig. 44-1): (1) the initiating process, (2) the generation of intrinsic thromboplastin, (3) the conversion of prothrombin to thrombin, and (4) the clotting of fibrinogen. Each step includes an indeterminable number of reactions, all of which appear to be stoichiometric, except

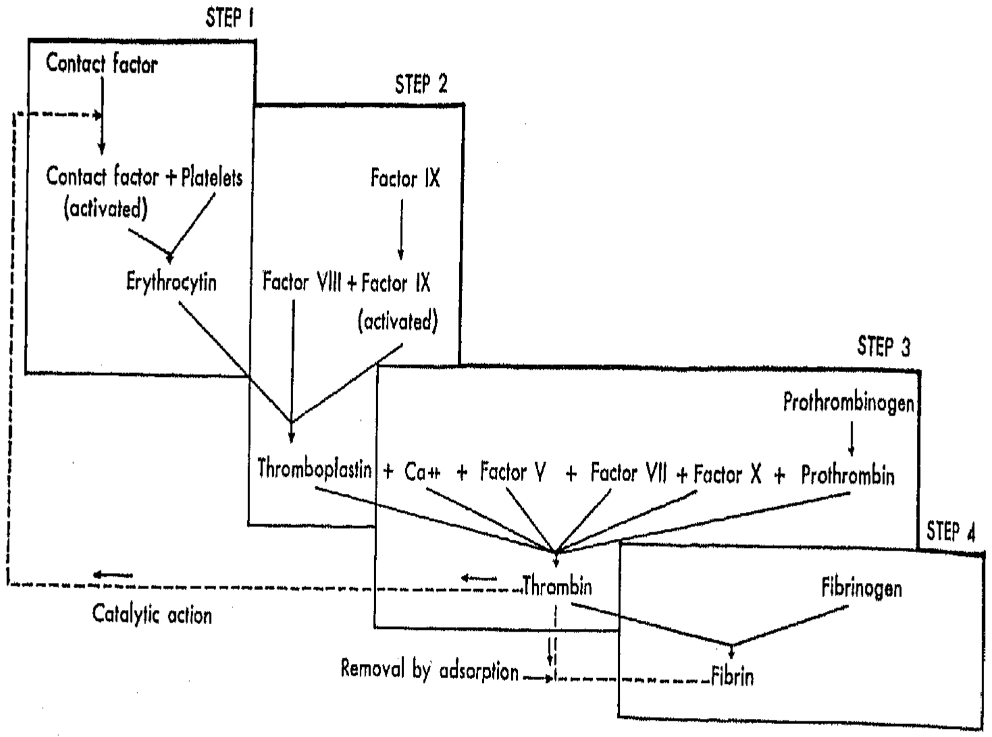


FIG. 44-1. Factors involved in the coagulation of blood. (From A. J. Quick, Ann. Int. Med., 55: 201, 1961.) Tissue thromboplastin can enter *Step 3* without requiring *Steps 1* and *2*. Heparin with a cofactor forms a strong antithrombin.

for step (4). Thrombin is a proteolytic enzyme which splits 2 fibrinopeptides from fibrinogen, thereby activating it to polymerize into fibrin, an insoluble protein of high molecular weight which forms the matrix of the clot. Thrombin has a second function: it activates a plasma constituent which has been designated as contact factor. This reaction is required to bring the platelets into the clotting reaction. It appears that a product is formed which resembles the clotting agent found in the erythrocyte and therefore has been named erythrocytin. Thrombin, by activating contact factor, brings about the formation of more thrombin and therefore serves as its own autocatalytic agent. Since thrombin is an enzyme, a small amount theoretically could convert all the circulating fibrinogen to fibrin and thus bring about massive thrombosis. Its prompt removal is therefore of utmost importance in controlling the chain reaction; this is accomplished physiologically by adsorption to fibrin surface. Thrombin is also removed or inactivated by a serum antithrombin, but its action is too slow to stop the autocatalytic reaction effectively. Heparin is a powerful antithrombin, but its concentration in blood is so minute that it is doubtful whether it contributes to the maintenance of the fluidity of the blood.

The over-all reactions of each step can be measured by a specific test. Steps 1 and 2 can be collectively estimated by the prothrombin consumption test. The blood is clotted under carefully standardized conditions and the prothrombin remaining in the serum is determined by the 1-stage prothrombin time test. The 3 important primary factors required for the formation of thromboplastin are platelets, factor VIII (antihemophilic factor), and factor IX (antihemophilia B factor or plasma thromboplastin component). Each of these 3 factors is present in great excess over its physiologic requirement; therefore even large variations in the concentrations are insignificant, and only marked reductions cause a bleeding state. A decrease of any one of these 3 factors brings about a low generation of thromboplastin. Results comparable to those of the prothrombin consumption test are obtained with the thromboplastin generation test of Biggs and Douglas. By appropriate, slight changes, either test can be made specific for the diagnosis of thrombocytopenia or hemophilias A or B. No drugs are known which increase platelets, factor VIII, or factor IX, but these deficiencies can be temporarily corrected by transfusion of fresh blood or plasma. Fresh frozen plasma, the term given to fresh plasma which is immediately frozen and stored at −20°C, is a most valuable agent in the treatment of hemophilia.

The key test to Step 3 is the 1-stage prothrombin time. In normal plasma the determinant of the prothrombin time is the concentration of free

or active prothrombin. The accessory factors V, VII, and X—also known as labile factor or accelerin, stable factor or proconvertin, and Stuart-Prower factor, respectively—are in excess and only affect the prothrombin time when they are decreased below a critical level.

Step 4 is measured by the thrombin time. In this test, the clotting time obtained by adding a standard solution of thrombin to the plasma of the patient is compared to the value obtained by adding the same amount to normal plasma. In *afibrinogenemia* the thrombin time is infinity, and in hyperheparinemia it is prolonged in proportion to the concentration of heparin. It can therefore be employed to determine quantitatively the heparin in the blood.

The clotting scheme presented is only to serve as a guide to the mechanics of the coagulation process. Factors not included are factor XI (plasma thromboplastin antecedent) and factor XII (Hageman factor). Their roles in coagulation are still uncertain. In addition to their participation in the generation of intrinsic thromboplastin, platelets are essential in clot retraction and perhaps in vasoconstriction, since they contain serotonin which chemically is 5-hydroxytrypt-

ARMAND J. QUICK

*Outstanding American investigator of the mechanism of blood clotting*

"The one-stage prothrombin time played a significant role in bringing about the renaissance of the study of blood coagulation as well as in transferring it from the laboratories of pure research to the clinic."

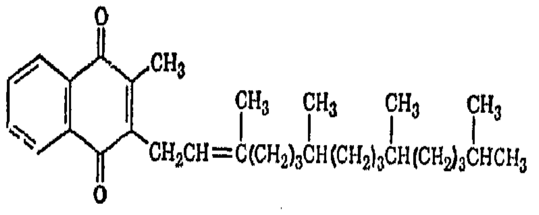
amine. Many drugs, including the sulfonamides, quinidine, and particularly Sedormid, cause thrombocytopenia in sensitized individuals. Curiously, an abnormal increase in platelets—thrombocythemia—brings about a bleeding state. Good results have been obtained with radioactive phosphorus, $P^{32}$, which depresses the platelet count and corrects the bleeding tendency.

## INDUCED ALTERATIONS OF COAGULATION

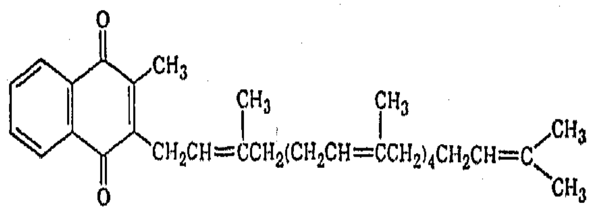
### Vitamin K.

In 1929 Dam, of the Biochemical Institute of the University of Copenhagen, demonstrated that chicks fed an inadequate diet manifested a bleeding tendency, and in 1935 he showed that the principle which cured the hemorrhagic condition could be obtained as an unsaponifiable nonsterol fraction of hog fat. Dam *et al.* (1936) and Quick (1937) discovered independently that vitamin K deficiency caused a marked decrease of prothrombin. During the years 1938 to 1940 the structure of this substance was determined and called "Koagulations-Vitamin," hence vitamin K.

Binkley *et al.* (1939) isolated pure vitamin K from alfalfa. It was called vitamin $K_1$, to differentiate it from a similar product obtained from sardine meal by the same investigators and called vitamin $K_2$. Each substance elevates the blood prothrombin level in man. The structures of the 2 vitamins are shown in the accompanying formulas.



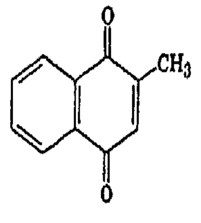
Phytonadione, U.S.P.
Vitamin $K_1$
(2-methyl-3-phytyl-1,4-naphthoquinone)



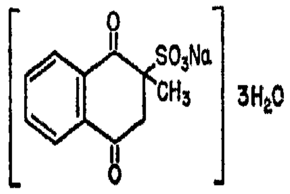
Vitamin $K_2$
(2-methyl-3-difarnesyl-1,4-napthoquinone)

Almquist and Klose (1939) showed that various simple naphthoquinones such as are present in the molecules of vitamins $K_1$ and $K_2$ exhibited vitamin K activity. Further studies demonstrated that 2-methyl-1,4-naphthoquinone (fraction from the molecule of vitamin $K_1$) was very active in elevating the prothrombin blood level in man. This comparatively simple compound, commonly referred to as *synthetic vitamin K* or *menadione*, is used clinically for vitamin K therapy. It is official in the Pharmacopeia.

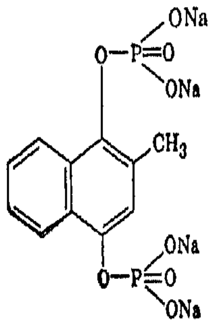
**Menadione, U.S.P.** Menadione occurs as a yellow, crystalline, odorless powder. It is slightly soluble in water. To make the compound available parenterally, the Pharmacopeia recognizes a *sodium bisulfite* derivative of menadione and also *menadiol sodium diphosphate*. The structures of the 3 compounds are shown in the accompanying formulas.



Menadione, U.S.P.
(2-methyl-1,4-naphthoquinone)



Menadione Sodium Bisulfite, U.S.P.
Soluble Synthetic Vitamin K



Menadiol Sodium Diphosphate, U.S.P.
Synkayvite Sodium Diphosphate

**The action of vitamin K.** The basic biochemical action of vitamin K has not been elucidated. It supplies the naphthoquinone derivative for a mitochondrial oxidation-phosphorylation system, but no clue has been offered as to how this is related to the production of clotting factors. When vitamin K deficiency occurs, the prothrombin time promptly becomes prolonged and the prothrombin activity, as measured by the 2-stage method, decreases. Actually factor VII is depressed first, and the subsequent decrease of prothrombin is quantitatively dependent on the level of the former. It is unlikely, however, that factor VII is an intermediate in the formation of prothrombin because in hereditary factor VII deficiency the prothrombin concentration is normal.

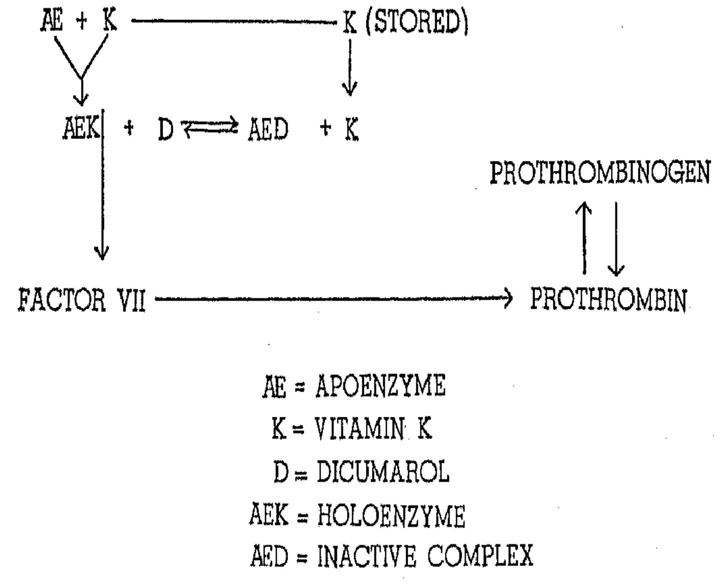


FIG. 44-2. The probable mechanism of bishydroxycoumarin (Dicumarol) action

A simple practical scheme summarizing the probable role of vitamin K is given in figure 44-2. Vitamin K furnishes the prosthetic group (*K*) which with an apoenzyme (*AE*) forms the holoenzyme (*AEK*). This agent appears to be directly involved in the synthesis of factor VII. A number of vitamin K antagonists, of which bishydroxycoumarin (Dicumarol, *D*) is the prototype, replace the *K* group to form the inactive *AED*. The effect is the same as in vitamin K deficiency. The synthesis of prothrombin, being secondary to the formation of factor VII, only drops when the latter is decreased. In adult man prothrombin exists in a partly free and partly inactive state. The inactive prothrombin constitutes about 75 per cent of the total. It may be regarded as a reserve; as the free prothrombin is decreased, the inactive prothrombin reserve is depleted.

In the adult dog, only 0.5 μg. of vitamin $K_1$/kg. daily is needed to maintain a normal prothrombin level, whereas in the growing pup, the requirements are over 50 times greater. One may assume that these findings also apply in the human. Because natural vitamin $K_1$ is poorly absorbed from the intestines and because of the high metabolic demand of vitamin K in the fast-growing baby, hypoprothrombinemia frequently occurs in the very early neonatal period. By supplying extra vitamin K to the mother prior to parturition, serious hypoprothrombinemia in the newborn can be prevented. For this purpose, menadione, menadione bisulfite, or menadione sodium diphosphate in small doses (2 to 5 mg. daily) can be employed with safety. Large doses of synthetic vitamin K compounds block the glucuronic acid conjugation mechanism and thus prevent the formation of bilirubin diglucuronide, resulting in *kernicterus.*

In obstructive jaundice and also in sprue, vitamin K deficiency readily occurs and results in a fall of factor VII; this in turn leads to a decrease of free prothrombin and prothrombinogen. The restoration of the prothrombin level is readily achieved by vitamin K. For this purpose, the synthetic vitamin K compounds have the advantage of being water soluble and easily absorbed from the intestine in the absence of bile. Neither vitamin K nor its analogs corrects hereditary hypoprothrombinemia or deficiencies of factors V, VII, and X.

### Pharmacologic response of bishydroxycoumarin.

Attention was called by Pfeiffer to the fact (1948) that the pharmacologic response to certain drugs may be due to an optimal spacing of active prosthetic groups in their molecules. Thus, optimally placed substituent groups in the molecules of pharmacologically active compounds may either enhance or block the action of enzyme systems or compete at active receptor sites with hormones. Consonant with this concept, it is of interest to note that the molecule of vitamin K has 2 active oxygen atoms at positions 1 and 4 on the naphthalene ring; the span of which is 6.4 Å. The active coumarins, used in prolonging the clotting time of blood, also contain 2 oxygen atoms in the 1 and 3 positions in the coumarin ring. The span between these active oxygen atoms is 6.1 Å. Extending the concept to the indanediones, which are used similarly to the coumarins, they contain 2 active oxygen atoms at positions 1 and 3 with a span of 5.9 Å. Thus, the pharmacologic concept of "exactness of fit" of the molecular structure, emphasized so frequently in the pharmacology of the autonomic nervous system, appears to have applicability in our concepts of modifying the clotting time of blood with drugs.

The action of bishydroxycourmarin and its relation to vitamin K is presented in figure 44-2. The drug appears to act as a true antimetabolite. It replaces the functional prosthetic group *K* in the holoenzyme *AEK* by a non-functioning group *D*. The larger the dose of bishydroxycoumarin, the more the functional holoenzyme is decreased and the more severe the depression of prothrombin activity. Since the reaction is reversible, the holoenzyme can be easily restored. Natural vitamin $K_1$ is much more effective in counteracting coumarin drugs than the synthetic analogs such as menadione.

### The therapeutic uses of menadione and vitamin $K_1$.

Menadione is used routinely antenatally in obstetrical practice. The newborn exhibits hypoprothrombinemia, and this may cause hemorrhagic manifestations. If the mother is given 1 to 2 mg. of menadione daily for 1 to 2 weeks before delivery, the prothrombin level as measured by the 1-stage test is normal. Hellman and Shettles (1942) showed a marked reduction in infant mortality and hemorrhagic disease when menadione was administered to the mother prophylactically. Retinal hemorrhage occurred in 25 per cent of the untreated cases. When menadione was given just 4 days antepartum, the incidence was reduced to 4 per cent. These observers recommend a routine daily medication with menadione for 2 weeks prior to delivery.

Menadione has been used prophylactically to prevent neonatal hypoprothrombinemia. Lehmann (1944), who studied 30,000 full-term infants, reported an infant mortality reduction of 1.6 per thousand births when menadione was given prophylactically within 1 hour after birth. If the mother is in a good nutritional state and has received vitamin K antenatally, vitamin K need rarely be given to the infant. If hemorrhage occurs, vitamin $K_1$ should be given parenterally.

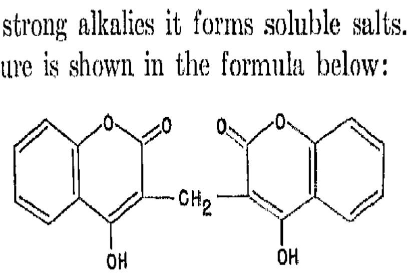
Hypoprothrombinemia in obstructive jaundice was a common cause of fatal postoperative bleeding prior to the discovery of vitamin K. Menadione and the other analogs effectively correct the vitamin K deficiency. Allen and Livingstone (1941) employed 2 mg. of menadione 4 times a day. With the availability of natural vitamin $K_1$ (Mephyton) for intravenous use, prompt correction can be obtained from a dose of 5 to 10 mg.

**Dosage, fate, and untoward effects.** Menadione and its derivatives, menadiol sodium diphosphate (Synkayvite) and menadione sodium bisulfite (Hykinone), are sufficiently water soluble to insure absorption from the intestines even in the absence of bile salts. Hoskin *et al.* (1954) studied the urinary excretion products of menadione in the rat. For the most part, the compound appears to be excreted as 2-methyl-1,4-dihydroxynaphthalene-1,4-diglycuronide and 2-methyl-4-hydroxy-1-naphthyl sulfate. A daily dose of 2 to 5 mg. of any of the 3 compounds is usually adequate, but the effect should be checked by a 1-stage prothrombin time. When given in therapeutic doses, menadione and its derivatives are devoid of toxic action and undesirable side effects. It is essential that excessive dosage be avoided in the newborn for reasons previously stated.

## AGENTS PROLONGING THE CLOTTING TIME OF BLOOD

### The anticoagulant coumarins.

Schofield in Canada (1922) and Roderick (1929) in the United States demonstrated that hemorrhagic diathesis in cattle occurred when they ingested improperly-cured common sweet clover hay or silage. This condition was shown to be due to prothrombin insufficiency by Roderick (1931), Quick (1937), and Campbell and Link (1941). Campbell and Link showed that the substance responsible for the hemorrhagic diathesis present in the spoiled sweet clover was a coumarin derivative. The compound isolated and later synthesized as bishydroxycoumarin is a colorless, crystalline solid, relatively insoluble in water. With strong alkalies it forms soluble salts. The structure is shown in the formula below:



Bishydroxycoumarin, U.S.P.
Dicoumarol (Dicoumarin)
[3,3′-methylenebis-(4-hydroxycoumarin)]

As in vitamin K deficiency, the first effect of the drug is a depression of factor VII, and this is measured quantitatively by the basic 1-stage prothrombin time. When a satisfactorily potent thromboplastin reagent which gives a prothrombin time of 12 ± 0.5 seconds is used, the free prothrombin begins to decrease when the prothrombin time is reduced to about 20 seconds. The theoretical therapeutic range is a prothrombin time of 20 to 25 seconds. The active prothrombin is then reduced to approximately 50 per cent of normal. This represents the maximal depression of coagulability consistent with relative safety from hemorrhage. It explains the success for the empirical practice of keeping the 1-stage prothrombin time at 2 to 2.5 times normal.

Factors IX and X are also depressed by the coumarin drugs, but this effect is again preceded by a fall in the concentration of factor VII. Therefore, by controlling the level of factor VII, undue depression of prothrombin and factors IX and X is easily avoided. Since factor VII is accurately measured by the 1-stage prothrombin time, the test remains indispensable for the control of anticoagulant therapy.

Bishydroxycoumarin and the other coumarin drugs discussed in this chapter, as well as several indandione compounds, have the same basic action. With any of these, the *AEK* enzyme system can be depressed and maintained at any desired degree, as measured by the prothrombin time. The maintenance dose of a drug is determined by its absorption from the intestinal tract, its affinity for the apoenzyme, and its rate of detoxication and excretion. Since all are vitamin K antagonists, the effect of the drug is also influenced by the amount of vitamin K stored in the body and the amount of vitamin K in the diet. All these factors must be taken into consideration. Thus, diarrhea may markedly diminish the amount of the drug absorbed, and liver or kidney damage may significantly retard the excretion and thereby intensify and prolong its action. A drastic change in diet, such as greatly increasing the vitamin K content, may cause a reduction in the prothrombin time. Infection may intensify the action of the coumarin drugs, and if a patient is treated with aspirin, which itself depresses factor VII, there is a further depression of prothrombin activity.

Although aspirin causes a slightly prolonged prothrombin time, the depression is not severe enough to produce a bleeding state. The gastrointestinal bleeding associated with aspirin is not related to its hypoprothrombinemic effect.

*Toxicologic effects of bishydroxycoumarin.* The coumarin drugs are strikingly free of side reactions. The one untoward effect is hemorrhage, but even this rarely occurs when the dose is so regulated that the prothrombin time does not exceed 2.5 times normal. This guide is valid, however, only when a potent thromboplastin free of factor VII is employed. Probably most of the cases of serious bleeding can be attributed to faulty laboratory control, but hemorrhages may occur when the patient is within the therapeutic range. It is to be stressed that when the prothrombin time is prolonged over 20 seconds, a potential bleeding state is induced. Any trauma is therefore apt to result in hemorrhage. A silent peptic ulcer may begin to bleed, and unexplained bleeding can lead to the disclosure of unsuspected early malignancies. Hematuria, which is a common form of bleeding, may be secondary to minor renal injury. Interestingly, hemarthrosis, deep intramuscular bleeding, and epistaxis rarely occur.

The effect of bishydroxycoumarin and related drugs can easily be reversed by vitamin K. For this, vitamin $K_1$ is far more effective than the synthetic analogs. Interestingly, it takes at least 24 hours to depress prothrombin activity with a coumarin drug, but vitamin $K_1$ will reverse the process, *i.e.*, replace *AED* with *AEK*, in about 4 hours. There are 2 preparations available of vitamin $K_1$ to combat hemorrhagic manifestations that occur in anticoagulant therapy. One of these, Mephyton (phytonadione emulsion), is a 5 per cent emulsion of the vitamin in an aqueous medium containing 1 per cent lecithin. It is also available in 5-mg. tablets. For reversal of prolonged prothrombin time without bleeding, 2 to 4 mg. of Mephyton are given orally or intravenously. For minor bleeding 5 to 10 mg. are required. For major hemorrhage 50 mg. or 1 ml. of the emulsion is given intravenously. It generally restores the prothrombin level to normalcy in 3 to 6 hours. The other product is vitamin $K_1$ oxide, which is also a suspension. Since its action is slower and less dependable, Mephyton is the drug of choice.

Liver function tests have been carried out repeatedly on patients receiving the drug clinically. There has been no evidence of damage (Bingham *et al.*, 1943). The blood picture, blood chemistry, and renal function tests are not affected by the therapeutically effective doses of the drug. The biological transformation products of bishydroxycoumarin in man are unknown.

Doses of coumarins greatly in excess of amounts used clinically cause severe toxic reactions in experimental animals. Rose *et al.* (1942) showed central necrosis of liver in rats resulting from repeated doses. Intravenous fatal doses of bishydroxycoumarin produce death in animals through liver damage. The fatal dose is 40 mg./kg., and the animals exhibit a dark and congested liver (Wakim *et al.*, 1943).

Bingham *et al.* (1941) were the first to note capillary dilatation in experimental animals that received large doses of bishydroxycoumarin. It has been shown that levels of bishydroxycoumarin far in excess of those necessary for anticoagulant activity exhibit a marked depressant effect on the isolated perfused heart. It was demonstrated that bishydroxycoumarin inhibited DPNH oxidase activity of heart muscle preparations. Wroblewski and Manso (1958) stated that bishydroxycoumarin administered to a patient with acute myocardial infarction may result in serum enzyme activity elevations independent of changes resulting from the myocardial necrosis. Bishydroxycoumarin-induced changes in serum transaminase are usually characterized by a greater increase in serum glutamic pyruvic transaminases (SGP-T) than in serum glutamic oxaloacetic transminases (SGO-T). In myocardial infarction the predominant increase is in SGO-T activity. These data should enjoin one to interpret with caution transaminase activity values during anticoagulant therapy. Other drugs are also capable of befogging interpretation of transaminase activities.

*Clinical use of bishydroxycoumarin.* Various workers have demonstrated the capacity of bishydroxycoumarin to delay intravascular thrombosis induced in laboratory animals. This suggests a field of clinical usefulness of bishydroxycoumarin similar to that of heparin. Bishydroxycoumarin is not capable of resolving thrombi or emboli which have already formed. Its action is preventive.

Bishydroxycoumarin is used alone or with heparin in the treatment of *postoperative thrombophlebitis* and *pulmonary embolism.* It is valuable in *acute embolic* and *thrombotic occlusions* of peripheral arteries. It is used in coronary occlusion.

Bishydroxycoumarin is contraindicated in all persons who are bleeding from any cause. It is not recommended in patients with hepatic disease or impaired renal function. In these conditions the effect of the drug is markedly accentuated.

Van Cauwenberge and Jaques (1958) demonstrated that rabbits treated with bishydroxycoumarin and ACTH died of hemorrhage. They did not die with either therapy alone. Cortisone and desoxycorticosterone did not produce death in animals treated with bishydroxycoumarin. They reported 2 cases of hemorrhage, 1 fatal, resulting from the use of ACTH in patients on the "coumarins" as anticoagulant therapy. It is clear that the use of ACTH in a patient on anticoagulant therapy with the coumarins is interdicted.

Spontaneous hemorrhage with anticoagulant therapy may stem from many causes. Hormonal and neuronal factors may affect the blood vessels and induce bleeding. Jaques (1962) in a comprehensive study revealed that rabbits treated with bishydroxycoumarin experienced internal hemorrhage when exposed to stress reactions such as insulin convulsions, or upon the administration of histamine, reserpine, epinephrine, and $P^{32}$.

Bishydroxycoumarin and related drugs can only be used effectively and safely when controlled by satisfactory 1-stage prothrombin time determinations. A generally accepted procedure is as follows:

*First day:* Check prothrombin time and if found normal, administer 5 mg./kg. (200 to 300 mg.) of bishydroxycoumarin orally.

*Second day:* Check prothrombin time and if prolonged to 50 per cent of normal or less, administer 100 to 200 mg. of the drug.

*Third and subsequent days:* The prothrombin time is determined and if found prolonged to more than twice the normal, the dose is omitted or reduced. In normal adult men, the maintenance dose is usually 50 to 75 mg. daily. The patient should be instructed to observe the color of his urine, as hematuria is the most common form of bleeding.

Allen *et al.* (1947) reported their experiences with bishydroxycoumarin in 2307 surgical and medical cases where the drug was used alone or with heparin. On the whole their observations were very favorable. They observed serious bleeding from wounds in only 2 per cent of their cases.

The use of bishydroxycoumarin in 352 cases of postoperative venous thrombosis reduced the incidence of subsequent thrombosis and pulmonary embolism from an expected 88 to 9. Among other findings, extremities were saved for 91 per cent of patients with arterial emboli and for 81 per cent with arterial thromboses when the anticoagulants were started early and supplemented by other therapy.

Brambel and Loker (1944) found bishydroxycoumarin useful in the treatment of post-traumatic arteriosclerotic and frost bite gangrene.

Wise *et al.* (1949) reported their findings of thromboembolic complications following surgery with and without bishydroxycoumarin therapy. Their observations include over 12,000 patients. Their data showed a significant reduction in the incidence of venous thrombosis when bishydroxycoumarin was employed. Fibrinogen determinations revealed no evidence of toxicity from bishydroxycoumarin. They emphasize the necessity for meticulous standardization of the laboratory procedure for gauging the bishydroxycoumarin effect if the best results are to be achieved in the prophylaxis program.

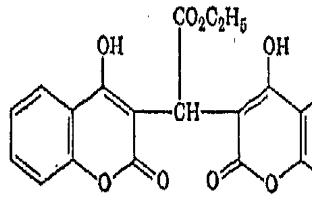
Of special interest is the study of bishydroxycoumarin in acute coronary thrombosis (Peters *et al.*, 1946). They observed an increased clotting tendency in most of their coronary patients. They studied 110 cases of coronary thrombosis with myocardial infarction; 50 patients were Dicumarolized, and 60 were not given the drug. Their observations extended over 2½ years. In the patients receiving the anticoagulant the occurrence of embolic phenomena was reduced to ⅛ and the mortality rate to ⅙ of those in the untreated patients. These results have been extended and confirmed.

Schilling (1950) studied 120 cases of myocardial infarction. Half received anticoagulants, and half did not. The incidence of thromboembolic complications in the control group was 25 per cent. In the treated group the incidence was 5 per cent. Indeed these benefits are both clinically and statistically significant. These findings were substantially confirmed by Wright *et al.* (1954), in a study of 1031 cases of myocardial infarction with and without anticoagulant therapy. Thromboembolic phenomena occurred in 29 per cent of the control group and in only 9 per cent of the treated patients. They state, "There is a real risk to the patient in waiting for the course to worsen or the first thromboembolic complication to develop before using anticoagulants." Seaman (1959) holds the view that in reports to date, death has occurred from 2 to 5 times more frequently in nontreated patients than in those treated with anticoagulants. Further recurrent infarcts are recorded from 2 to 19 times more often in untreated patients than in patients treated with anticoagulants.

Further confirmatory studies were conducted by Thomes *et al.* (1961) on 156 patients with coronary artery disease. Of these, 84 were observed after cessation of treatment. An estimated 803 per 1000 patients on continuous therapy remained recurrence-free after 60 months. On the other hand, only 365 per 1000 remained recurrence-free for 60 months after discontinuance of treatment. They caution against the danger of stopping treatment.

The rationale of treatment appears to rest on a firm experimental basis. Wright *et al.* (1952) reported increased speed of recanalization of thrombosed femoral arteries in dogs, which were promptly medicated with coumarins, contrasted with untreated dogs with similar lesions. Consonant with those observations are the studies of Taylor and Essex (1959). They showed that the recanalization of experimentally produced thrombosis in rabbit's ear veins occurred much more rapidly when the coumarins were administered than in animals without treatment. Implicit in these reports, clinical and experimental, is the fact that the use of anticoagulant therapy in cases of coronary insufficiency with infarction is established.

**Ethyl Biscoumacetate (Tromexan Ethyl acetate, Tromexan).** Tromexan is a synthetic anticoagulant of the coumarin series. It was originally synthesized by Link and his associates in 1942. The compound is ethyl-3,3-bis(4-hydroxycoumarinyl)-acetate. Its structure is shown in the following formula.



Tromexan

Tromexan is a colorless, crystalline powder. It is 4 to 6 times more water soluble than bishydroxycoumarin. The acute and cumulative toxicity has been investigated by Burke and Wright (1951) and Gruber *et al.* (1951).

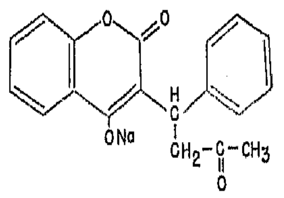
Normal control subjects were given 1.2, 1.5, and 1.8 gm. of Tromexan in single doses. Twenty-four hours later prothrombin times were uniformly at a level of 25 to 35 seconds with the larger doses. The maximal change occurred in 28 to 36 hours and the return of the prothrombin time to normal took place at 60 to 72 hours. No evidence of toxic symptoms was manifested by this group.

Burke and Wright (1951) used Tromexan in 50 patients with thromboembolic disease. There was almost a complete freedom from delayed toxic phenomena. Using 0.6 to 0.9 gm. daily, satisfactory reduction of the prothrombin time for prophylaxis was achieved.

The British investigators Burt *et al.* (1949) found that Tromexan could be administered to patients with thromboembolic disease for long periods of time, reducing the prothrombin activity 50 per cent without cumulative effect.

Tromexan has the same basic action as bishydroxycoumarin, warfarin sodium, phenindione, and other drugs of this series in that it depresses factor VII first and prothrombin later (Noren and Quick, 1963). It is rapidly absorbed from the intestinal tract and readily detoxicated and eliminated by the human. In the dog its effect is more prolonged. Its maintenance dose is over 5 times that of bishydroxycoumarin. Because of its rapid elimination, it is more difficult to keep a constant depression of prothrombin activity. The contraindications to Tromexan are the same as those of bishydroxycoumarin. Severe bleeding can occur when the dose is not properly regulated.

**Warfarin Sodium, U.S.P. (Coumadin Sodium).** This compound is another 4-hydroxycoumarin anticoagulant synthesized by K. P. Link. The name warfarin is derived from the first letters of the Wisconsin Alumni Research Foundation. The compound is used extensively as a rodenticide because of its potency in producing fatal internal hemorrhage in rodents. Holmes and Love (1952) reported an account of an army inductee who attempted suicide with warfarin. Hemorrhagic phenomena followed the marked reduction of prothrombin produced by the agent. This syndrome confirmed in man that the action of warfarin was similar to that of bishydroxycoumarin. The hypoprothrombinemic potency of warfarin is about 40 times greater than bishydroxycoumarin. Its relation to bishydroxycoumarin is shown by the formula:



Warfarin Sodium, U.S.P.
Coumadin Sodium
[3-($\alpha$-acetonylbenzyl)-4-hydroxycoumarin sodium]

Warfarin sodium is a white, crystalline powder which is freely soluble in water. The presence of the phenolic hydroxyl group in the molecule makes it possible to solubilize warfarin as its sodium salt.

The indications for warfarin therapy are identical with those of bishydroxycoumarin. Its advantages appear to lie in the rapid production of hypoprothrombinemia and the greater predictability of response. In addition, owing to its water solubility, warfarin is available for intravenous injection. Clatanoff *et al.* (1954) found the latent period of action of warfarin to be shorter than those of bishydroxycoumarin. It was similar to that of Tromexan, but the duration of hypoprothrombinemia was much longer.

Shapiro and Weiner (1951) suggested that with all anticoagulants some resistant cases may be encountered. These, however, are fewer when the potency of the anticoagulant is great. It is therefore to be anticipated that fewer resistant cases will be encountered with warfarin than with bishydroxycoumarin or Tromexan.

Danford *et al.* (1958) compared the efficacy of warfarin with that of bishydroxycoumarin in a series of patients requiring anticoagulant therapy. Their criterion was based upon the incidence of "escape periods," *i.e.*, shifts in prothrombin level after the maintenance dose is established and the patient is stabilized. The incidence was 5 per cent with warfarin and 9 per cent with bishydroxycoumarin. They observed no other untoward effects with warfarin and found vitamin K an effective antagonist to its action.

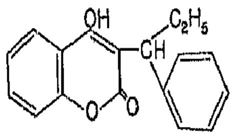
Blumberg *et al.* (1960) showed that therapeutic doses of warfarin fed to lactating rats had no effect on the clotting time of blood of the nurslings. There were no other deleterious effects. Toxic or lethal doses of the anticoagulant were excreted in the milk and extended the clotting time of the blood of the nurslings to a limited extent.

Hemorrhagic manifestations under warfarin therapy may be combated by the use of vitamin $K_1$ emulsion and transfusion.

Warfarin sodium is available in 25-mg. tablets and in ampules containing 75 mg. in 10 ml. A single intravenous dose of 75 mg. will usually produce hypoprothrombinemia (25 to 45 seconds whole plasma) within 12 to 18 hours. It usually persists for 5 to 6 days. An oral dose of 25 to 50 mg. elicits a hypoprothrombinemia which lasts about 72 hours. As a rule, therefore, medication is given at 3-day intervals.

It appears to the authors that warfarin exhibits many of the characteristics of the ideal anticoagulant and elicits few untoward side effects. Its general use appears to be increasing rapidly. Although it is comparatively new, clinical reports on its use are promising.

**Phenprocoumon, (Liquamar).** This compound is another 4-hydroxycoumarin derivative with potent anticoagulant activity. The structure of phenprocoumon is shown in the formula. This compound is also referred to as *Marcumar*.



Phenprocoumon
Liquamar
[3-(1′-phenylpropyl)-4-hydroxycoumarin]

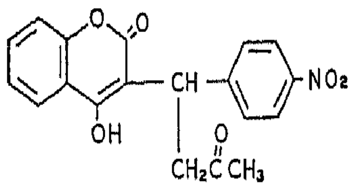
Phenprocoumon is a white, crystalline powder which is sparingly soluble in water.

Bourgain *et al.* (1954) studied phenprocoumon in rabbits and observed that a prolonged hypoprothrombinemia was evoked by its administration. Their experiments indicated that the compound was suitable for anticoagulant therapy in man.

In man, hypoprothrombinemia persisted for 5 days after a single oral dose of phenprocoumon. This optimal dosage schedule for phenprocoumon as determined by Bourgain *et al.* was 21 mg. the first day and 9 mg. the second day. Maintenance dosage was 3 mg. (1 tablet) daily. There appeared to be some tendency for the effect to accumulate with respect to time on the same dosage schedule. The onset of action of phenprocoumon was found to be intermediate between that of bishydroxycoumarin and that of Tromexan.

Gold and Lilley (1959) evaluated phenprocoumon in 111 patients requiring short-term anticoagulant therapy. They used "loading doses" of 30 mg., and 21 mg. if the prothrombin time was somewhat prolonged above normal. Satisfactory response was achieved on the average in 42 hours in 77 per cent of the patients. The maintenance dose varied between 1.5 and 12 mg. daily; 4 mg. was the average. Hemorrhagic complications occurred in 3.6 per cent of the patients; in each instance vitamin K served to terminate bleeding. They state: "Phenprocoumon produced a satisfactory state of blood hypocoagulability during short term therapy of thrombovascular disease states."

**Acenocoumarol (Sintrom).** Sintrom is an anticoagulant of the coumarin series with an extraordinarily high potency. Its structure is shown in the formula:



Acencoumarol
Sintrom
[3-($\alpha$-acetonyl-4-nitrobenzyl)-4-hydroxycoumarin]

Sintrom is a white, crystalline powder which is sparingly soluble in water. It is of interest that the formula contains a nitro group. There are few commonly used drugs containing a nitro group; one is the antibiotic chloramphenicol.

Sintrom was introduced into therapy in the United States after pharmacologic and clinical studies had been conducted in Europe. Montigel and Pulver (1955) reported from their animal studies that Sintrom was a highly active anticoagulant with a short period of action. The compound when administered first depresses the level of factor VII and to a lesser degree the level of prothrombin. After continued treatment, each level is equally affected. It is rapidly excreted like Tromexan, but unlike Tromexan it is not metabolized but excreted unchanged by the kidney in the urine. Neill *et al.* (1957) suggest that Sintrom is intermediate in its action between

Tromexan and bishydroxycoumarin and exhibits certain advantages over each of these drugs.

Neill *et al.* (1957) studied Sintrom in 156 patients requiring anticoagulant therapy. Sintrom produced a therapeutic prothrombin level in most patients within 36 hours after a "loading" dose. The initial dose is usually 16 to 28 mg. The average maintenance dose in this series was 5.9 mg. daily. Neill *et al.* consider that 2 mg. of Sintrom is the therapeutic equivalent of 25 mg. of bishydroxycoumarin. They found the dosage level reasonably constant in a given patient, but variable from patient to patient, as with other anticoagulants. They were favorably impressed by the rapid period of elimination of Sintrom.

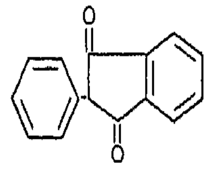
The observations of Neill *et al.* were confirmed by Rullo *et al.* (1958) in 100 hospitalized patients. They found that Sintrom was dependable and that its effects were predictable as an anticoagulant. Hemorrhagic phenomena were manifested in 5 per cent of the patients. No other toxic manifestations were encountered

The same indications, precautions, and antidotal measures which have been discussed with the other coumarin derivatives obtain with Sintrom.

It appears that another and strongly competitive anticoagulant of the coumarin type has taken its place in the armamentarium.

### The anticoagulant indandiones.

**Phenindione (Hedulin).** Hedulin is an indandione anticoagulant used orally in the conditions in which the coumarins are used. Its chemical structure is shown by the formula:



Hedulin
(2-phenyl-1,3-indandione)

Hedulin occurs as pale lemon-colored crystals. It is nearly insoluble in water.

The action of Hedulin as an anticoagulant is more rapid and less prolonged than that of bishydroxycoumarin. Cumulative action is not encountered, and the compound is readily dissipated when treatment is withdrawn. Hemorrhagic manifestations which may occur with Hedulin therapy are combated readily by the use of vitamin $K_1$ emulsion. In the body, Hedulin is partially catabolized and partially excreted unchanged by the kidneys.

The maximal hypoprothrombinemia is achieved in 28 hours after the administration of Hedulin. This is about half the time that is required for the same degree of activity with bishydroxycoumarin. Millar *et al.* (1958) studied the disappearance of Hedulin from the plasma of animals after intravenous injection. Hedulin disappeared more rapidly than bishydroxycoumarin. Considerable quantities of Hedulin were found in the liver and intestines 1 hour after administration. Upon oral administration, after 4 to 6 hours 50 per cent of the drug was recovered from the intestine and only 10 to 20 per cent was found in the liver.

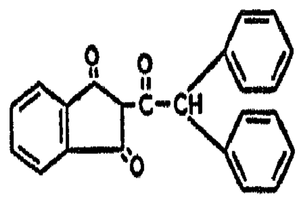
Hedulin is available in 50-mg. tablets. The initial daily dose is 200 to 300 mg. The average maintenance dose is 50 to 100 mg. daily.

The incidence of hemorrhagic manifestations with Hedulin is small. Blaustein *et al.* (1953) observed an incidence of hemorrhage in only 0.75 per cent of 400 patients treated with Hedulin. The principal advantages of Hedulin appear to be the uniformity with which patients respond to its action, freedom from untoward effects, and absence of cumulative action. Kruesi and Schilling (1954) suggest that if with Hedulin therapy the prothrombin time is slightly prolonged beyond the desired effect, the dose of the drug should be reduced 50 per cent rather than discontinued.

Although many clinicians have reported the absence of untoward effects, either as kidney or liver damage, Brown and MacMillan (1954) encountered 2 cases of *agranulocytosis* with Hedulin therapy. One of these was fatal. Another case of agranulocytosis was mentioned by Townsend *et al.* (1953). A patient was seen by Makous and VanderVeer who developed a serious sensitivity reaction to Hedulin; the symptoms included *skin rash, hepatitis, jaundice, a leukemoid blood picture,* and *anemia.*

It appears to the authors that no special advantage can be achieved with Hedulin that cannot be duplicated by the use of one of the coumarins. Since serious and even fatal side effects have been encountered occasionally in the much smaller segment of patients using Hedulin than are medicated with the coumarins, its advantage as an anticoagulant remains to be established.

**Diphenadione, N.F. (Dipaxin).** This compound is the second indandione derivative introduced as an anticoagulant. The onset of activity with diphenadione is more rapid than with Hedulin. The structure of diphenadione is shown in the formula:



Diphenadione, N.F.
Dipaxin
(2-diphenylacetyl-1,3-indandione)

Diphenadione occurs as a yellow, crystalline powder which is insoluble in water.

Pharmacologic studies with diphenadione in rabbits demonstrated that its principal activity is that of producing hypoprothrombinemia. Doses in the order of 50 mg./kg. induced effective prothrombin lowering within 48 hours which gradually returned to normal levels. Animals maintained on therapeutic levels of diphenadione for 13 weeks revealed no evidence of hematologic or other systemic toxicity.

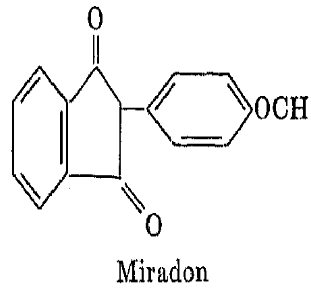
Diphenadione has been studied clinically as an anticoagulant in many carefully controlled series of patients. For example, Katz *et al.* (1954) found its action to be predictable and reproducible in a series of controlled observations. An initial dose of 30 mg. evoked satisfactory prothrombin levels within 41 hours. The second day 10 to 15 mg. is given, and maintenance is usually achieved by a daily dose of 2.5 to 5 mg. Field *et al.* (1955) consider the drug especially valuable for those patients who can have their prothrombin levels checked only at 2- to 3-week intervals.

Pascale and Olwin (1954), in a series of 80 patients in whom diphenadione was employed as an anticoagulant, found it to be an effective prothrombin depressant. Hemorrhagic phenomena occurred in only 2 per cent of the patients and no other toxic effects were encountered.

Katz *et al.* (1954) are of the opinion that diphenadione acts first on the stable component and later on the prothrombin itself.

Serious untoward effects do not appear to have been encountered with diphenadione therapy. Nausea, however, was reported in some early studies. The same indications, precautions, and antidotal measures which have been discussed under the other anticoagulants prevail with diphenadione.

**Anisinidione (Miradon).** Miradon is another anticoagulant that is an indandione derivative, as shown in the formula:



Miradon
(2-*p*-anisylindandione-1,3)

Miradon occurs as a white, crystalline powder that is sparingly soluble in water.

The principal pharmacologic response to Miradon is identical to that described for the previously discussed anticoagulants, namely, depression of the prothrombin activity of blood. The action of Miradon is prompt: prothrombin levels fall to the therapeutic level of 15 to 30 per cent in 48 to 78 hours. The action is of comparatively short duration, since prothrombin levels return to normal in 12 to 48 hours after the withdrawal of the drug.

Paul *et al.* (1959) found little difficulty in maintaining therapeutic prothrombin levels with daily doses of Miradon. Nausea, vomiting, diarrhea, proteinuria, agranulocytosis, or leukopenia have not been reported during Miradon therapy. Chromaturia of a transient nature has been observed. The same precautions and contraindications that apply to other systemic anticoagulants obtain with the use of Miradon. Similarly, its action is terminated by the intravenous injection of vitamin $K_1$ emulsion.

Miradon is supplied in 50-mg. tablets. The initial dose is 300 mg. on the first day, 200 mg. on the second day, and 100 mg. on the third day. Maintenance daily doses range from 25 mg. to 250 mg.; the usual daily dose is 75 to 100 mg.

**Bromindione, Halinone.** This compound is a potent anticoagulant. Chemically it is *p*-bromphenylindandione. It was studied by Singer *et al.* (1962), who claim it to be 3 times more potent than warfarin. The agent induced hypoprothrombinemia within 28 to 34 hours. The maintenance dose was 2 to 5 mg. daily. Side effects were claimed to be minimal.

**Choice of an anticogagulant.** It is apparent now that there are several useful anticoagulants available which emulate the activity of the first generally used drug of this class. Bishydroxycoumarin, warfarin sodium, phenprocoumon, and Sintrom (acenocoumarol) are coumarin derivatives and as a class are referred to as the *cou-*

*marins.* Hedulin and diphenadione are indandione compounds. These agents vary greatly in their degree of potency and hence in their dosage schedules. From the point of view of persistence of effect, the drugs may be divided into 2 main classes. Of those which are long-acting, warfarin sodium and Sintrom are representative. Tromexan and phenindione are the short-acting drugs. Bishydroxycoumarin occupies an intermediate position. A constant maintenance dose can be achieved more readily with the long-acting drugs. None can be designated as the safest because safety can only be attained by proper laboratory control. The availability of effective antidotal measures (vitamin $K_1$) assures means for increasing safety for all these drugs, but the most effective way is to determine accurately the daily maintenance dose by the prothrombin time and not to allow the latter to exceed 2.5 times the normal (table 44.1, page 711).

### HEPARIN

**Heparin Sodium, U.S.P.** *Heparin sodium is a mixture of active principles, having the property of prolonging the clotting time of blood in man or other animals.* It is standardized to contain 100 U.S.P. heparin units per milligram.

Heparin sodium is the hydrated sodium salt of a naturally-occurring complex organic polymer. The chemical constitution of heparin has not been definitely established. It appears to be a mucoitin polysulfuric acid (Jorpes, 1946). It is a polysaccharide consisting of hexosamine and hexuronic acid molecules esterified with sulfuric acid. The substance occurs as a white or lightly colored amorphous powder. It is very soluble in water; the aqueous solutions of heparin sodium are nearly neutral. The substance is prepared from liver or lung tissue. Recent studies have shown that the human lung contains 110,000 units of heparin/kg. of dry weight; bovine lung, 200,000; dog liver, 270,000; sea snails, 530,000; and mastocytomas of the dog, 950,000. The presence of the anticoagulant in large quantities in sea snails is surprising, since its anticoagulant properties are not needed in these organisms.

Heparin is secreted by the mast cells, which also secrete histamine. Heparin stains with toluidine blue. The concentration of mast cells in tissues parallels the staining reaction for the mucotin sulfuric acid or crude heparin.

**Mechanism of action of heparin.** Heparin, *per se*, is not an anticoagulant or an antithrombin, as shown by the observation that it does not inhibit the clotting of purified fibrinogen by thrombin. Likewise, it is not an antiprothrombin agent because a partially purified preparation of prothrombin is readily converted to thrombin even in the presence of an excess of heparin (Quick, 1936).

Heparin, with a cofactor which is a plasma protein found in the albumin fraction, probably an alpha globulin, forms a complex that has a powerful antithrombic action. This chiefly accounts for the anticoagulant activity of heparin and the prolonged clotting time when it is added to blood. It is doubtful whether heparin plays a role in preventing intravascular clotting. Normally, little or no free heparin is found in the blood, and the intravenous injection of such a powerful clotting agent as thrombin fails to stimulate the excretion of heparin into the blood.

Under controlled conditions the prolonged clotting time is proportional to the concentration of heparin, and if sufficiently high the blood becomes incoagulable. In the prophylactic employment of heparin as an anticoagulant against intravascular clotting, the clotting time is a simple and satisfactory means to control therapy. Heparin has other activities in addition to being an anticoagulant; these will be discussed elsewhere.

**Standardization of heparin sodium.** For many years after the isolation of heparin (McLean, 1916), the clinical use of the substance was thwarted by the numerous impurities present in the product. The crystalline barium salt was prepared and later the crystalline sodium salt was made. The crystalline sodium salt may serve as a standard to measure the anticoagulating action of commercial batches of heparin. Many methods of assay have been established. They depend upon the capacity of heparin to prevent the clotting of sheep or cattle plasma under standardized conditions. The U.S.P. directs the use of sheep plasma. This activity is compared with a standard heparin powder. The United States Pharmacopeial Committee has prepared a standard of *crystallized heparin sodium* for use in America.

One unit of heparin is approximately 0.01 mg. of the heparin sodium. Thus a dosage of 50 mg. supplies 5000 units.

**Clinical use of heparin.** Heparin is used clinically in the following conditions:

1. To prevent clotting during transfusion
2. To prevent postoperative thrombi

3. To combat phlebitis, thrombophlebitis, and pulmonary embolism
4. To maintain fluidity of blood during operations employing extracorporeal bypass

As heparin acts in the presence of blood to prevent thrombin formation, the substance will prolong the clotting time of shed blood. It has been found useful to prevent the clotting of blood in place of sodium citrate solution (Sappington, 1939).

Best (1938) showed that heparin inhibits the formation of thrombi produced by mechanical or chemical injury to the intima of large exposed veins. Experiments of this character stimulated the use of the substance clinically to prevent postoperative thrombi. Jorpes (1946) reported excellent results in the prevention of thrombi formation in cases where these might have been expected. Heparin is especially useful after surgery of the vascular system, brain, and central vein of the retina.

Engelberg (1954) used large subcutaneous injections of heparin in the prevention and treatment of thromboembolic disease. He points out that the viscosity of blood is diminished almost immediately upon intravenous injection of the drug. Furthermore, the reduction in blood viscosity persists after the coagulation time has returned to normal. Platelet adhesiveness was also diminished by heparin. These factors, in addition to the anticoagulant action of heparin, bespeak its value in the treatment of thrombophlebotic disease.

The principal untoward effect of heparin is the hemorrhagic tendency caused by the prolonged clotting time of the blood. If excessive bleeding at the site of operation, purpura, ecchymosis, hematuria, or other hemorrhagic manifestations occur, heparin should be discontinued. Its action may be checked by transfusion.

It is possible that heparin evokes a biphasic thrombogenic effect. Indeed, Ashwin (1962) demonstrated the effect in rats receiving intravenous doses of saline or heparin. When the clotting times returned to normal, formalin solution was applied to the jugular vein, and 4 hours later the veins were examined for clots. The heparinized animals showed 73.9 per cent thrombosis and the controls showed 58.6 per cent. A dose of heparin 1 minute before the operation reduced the incidence of thrombosis 16 per cent. The thromboses were not associated with platelet stickiness. Ashwin suggests that his data emphasize the danger of treating thromboembolic disease with inadequate doses of heparin.

Dragstedt *et al.* (1942) showed that salmine sulfuric acid (a protamine) inactivates the action of heparin *in vitro* and *in vivo*. Jorpes (1946) found that the intravenous injection of this protamine immediately caused the termination of hemorrhagic manifestations caused by heparin. If 5 to 10 ml. of a sterile 1 per cent solution of the protamine sulfate is given by vein, the coagulation time of the blood is brought instantly to normal. The pure protamine sulfate from herring or salmon is dissolved in dilute hydrochloric acid, pH3, and sterilized in an autoclave. Jorpes states: "It produces no undesirable reactions." Clinical experience is not completely in accord with this statement. For example, Weiss *et al.* (1958) noted that hypotension, bradycardia, and dyspnea may be encountered with therapeutic doses of protamine sulfate. Another agent which is employed to terminate the action of heparin is *toluidine blue*. This agent also may produce adverse effects such as hypotension, bradycardia, and cyanosis.

**Hexadimethrine bromide (Polybrene).** Polybrene, a heparin antagonist, has been withdrawn from the market; for a description of this drug, see the 5th edition, page 1080.

**Other uses of heparin.** Owing to the anticoagulant action on blood, heparin is useful in the treatment of *frost-bite*. Gangrene is often prevented by heparinizing the patient shortly after exposure to cold. Theis *et al.* (1951) recommended the use of heparin in sufficient levels to maintain the coagulation time at double the normal value while bishydroxycoumarin therapy is being instituted.

Griffith *et al.* (1952) employed heparin as well as other anticoagulants in congestive heart failure. The repository form of heparin injection was found most useful. They indicated that in a series of 416 cases heparin, as well as other anticoagulants, was useful in diminishing the incidence of thrombophlebotic phenomena.

Block *et al.* (1951) has shown that the injection of heparin will cause a clearing of alimentary lipemia and a redistribution of plasma lipoprotein fractions. It appears that heparin plays a role in lipoprotein metabolism. Although the mechanism of the lipid-clearing action of heparin has not been definitely delineated, certain recent studies serve to elucidate the phenomenon. Robinson and Harris (1959) demonstrated that lipase activity in rabbit plasma can be detected 20 seconds after an intravenous injection of heparin; the peak activity is achieved within 1 minute. Furthermore, the process of lipid clearing has been shown to be accelerated by increased oxygenation and diminished by rebreathing or the administration of sodium cyanide (LeQuire *et al.*, 1957). This action of heparin appears to be nonspecific. Synthetic anticoagulants, such as *sulfonated ovomucoid*, *sulfonated saponin*, and *sulfonated tannin* evoked antilipemic activity in rats which was independent of their anticoagulant action (Hladovec *et al.*, 1957).

Opdyke *et al.* (1955) failed to demonstrate convincingly any inhibitory effect of the injections of a heparin complex (butacaine heparin) on the incidence or severity of aortic atherosclerosis in chickens. Many clinical investigators have used heparin to reduce plasma lipids and to thwart the atherosclerotic process. Sublingual preparations of heparin have been used for this purpose. The use of heparin in the prevention or amelioration of the atherosclerotic process has not been established.

Heparin has been claimed to evoke an anti-inflammatory action. Dolowitz and Dougherty (1960) used intravenous heparin in the treatment of infected external otitis that had failed to respond to steroids and antibiotics. They achieved success in a significant number of cases. They assert that heparin combines with endogenous histamine, forming an innocuous complex. In selected cases of hay fever and asthma heparin also proved to be of value. It will be interesting to see whether or not these observations will receive general acceptance.

**Administration and dosage.** Heparin sodium is available in solution; each ml. contains 10 mg. of the substance. One ml. of this solution will prevent the clotting of 5 L. of plasma for 4 hours at 37°C. The solution is generally diluted with normal saline solution and given by intravenous drip (10 mg. in 100 ml.). A dose of 50 mg. (5000 units) given slowly (30 to 60 minutes) will prolong the clotting time of blood from 4 to 5 minutes to 15 to 30 minutes. This condition will obtain for about 2 hours. The compound is inactivated and excreted in the urine (Jorpes, 1946). Cho and Jaques (1955) extracted the enzyme heparinase from the livers of various animal species and also from human liver. The enzyme terminates the activity of heparin. The rate of heparin inactivation appears to be 50 per cent in 3 hours (Cho and Jaques, 1955). Heparinase was shown to be globulin-like in composition.

When the clotting time has returned to normal, the drug may be administered again. The patient usually requires an average of 10 to 15 mg. of heparin per hour on the first and second days and 5 to 10 mg. per hour on subsequent days. The most physiologic method of giving heparin is by continuous intravenous infusion (Jorpes, 1946). The heparin needs of different patients are subject to variation and should be modified according to the clotting time of the blood, which should be checked 2 or 3 times daily.

Heparin is not active when administered orally. DeTakats (1950) used 10 per cent heparin sodium solution intramuscularly. He found his results most favorable for anticoagulant therapy not exceeding 6 to 8 days.

Heparin is now available in a repository form for deep subcutaneous injection. The repository form of heparin contains gelatin, and this substance delays the absorption time and prolongs its action. The repository form of heparin may also be used with vasoconstrictors such as epinephrine to delay further absorption. The initial dose of repository heparin is 2 ml. (400 mg.), followed by 1 ml. (200 mg.) every 12 to 24 hours as indicated by the coagulation time of the blood of the patient. Monkhouse (1954) showed that larger doses of heparin are required intramuscularly, as compared to intravenously, to achieve the same concentrations of heparin in the blood for 6 to 8 hours. This is an indication that large intramuscular doses enjoy a different fate in the body. For example, the removal of the kidneys from animals results in the accumulation of heparin in the blood after intramuscular injection, but not upon intravenous administration.

**Synthetic heparin-like substances.** Several attempts have been made to synthesize compounds similar to heparin in structure and capable of prolonging the clotting time of blood. One of the substances which elicits a response similar to heparin is *Treburon*. Treburon is the *sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside*. It evokes about ⅓ of the anticoagulant potency of heparin sodium when administered intravenously to man. The dose is therefore 3 times greater than that of heparin. After extensive preliminary clinical trial the use of Treburon in man was abandoned because of the fact that occasionally patients receiving the drug developed varying degrees of *alopecia* and sometimes a delayed *diarrhea*. This is unfortunate because Treburon might have served as an inexpensive substitute for heparin.

Another similar anticoagulant available only for laboratory use is Mannuronate, which is sodium polyanhydromannuronic acid sulfate.

### Hemostatics

There are several substances which are used for local application to bleeding tissues to check the flow of blood. These are called hemostatics. The hemostatic agents frequently employed are absorbable gelatin sponge, fibrin foam, oxidized cellulose, and thrombin.

These agents, together with pressure, are useful in controlling bleeding after tooth extraction, in epistaxis, and in other surface bleeding. Their action is essentially mechanical and often is inadequate when the bleeding has an underlying cause, such as factor VIII deficiency (hemophilia).

**Absorbable Gelatin Sponge, U.S.P. (Gelfoam).** This product is a sterile, absorbable, water-insoluble, gelatin-base sponge. It is indicated in the control of capillary bleeding. For this purpose it is frequently moistened with thrombin solution before use. The sponge material is absorbable and may be left in place following the closure of an incision. The sponge is absorbed within 4 to 6 weeks. Contact with tissue does not produce excessive scar tissue formation or untoward cellular reactions.

Gelfoam is provided in jars containing sterile sections, 20 × 60 mm. Also, sections of 80 × 125 mm. are available.

**Fibrin foam.** This substance is a dry, sterile preparation of fibrin prepared from Fraction I of citrated normal human plasma as fractionated by Cohen's method. It is standardized by the National Institutes of Health.

Fibrin foam serves as a mechanical coagulant. In combination with thrombin, fibrin foam produces a chemical as well as a mechanical matrix for coagulation. The substance is used in brain surgery and surgery of the kidneys and liver where ordinary methods of hemostasis are ineffective. Fibrin foam is available ready for mixing with thrombin and isotonic salt solution prior to use.

**Oxidized Cellulose, U.S.P. (Hemo-Pak, Oxycel).** This substance is absorbable gauze or cotton. Chemically, oxidized cellulose is cellulosic acid.

TABLE 44-1

*Anticoagulants and Dosage*

| Coumarin and Indandione Derivatives | Average Doses (Controlled by Prothrombin Test) | | |
|---|---|---|---|
| | First dose | Second dose | Following |
| | | *mg.* | |
| Bishydroxycoumarin.... | 300 | 100–20 | 25–100 |
| Tromexan.............. | 1500 | 900 | 300–900 |
| Phenprocoumin......... | 21 | 9 | 3 |
| Warfarin sodium........ | 25–75 | 5–10* | 5–10 |
| Sintrom................. | 16–28 | 8–16 | 2–10 |
| Hedulin................. | 150 | 50–75 | 25–75 |
| Diphenadione, Dipaxin.. | 18 | 9 | 3–6 |
| Miradon................ | 300 | 200 | 75–100 |

* Administered at 3-day intervals.

Oxidized cellulose is markedly hemostatic when applied to tissues from which blood is oozing. It is absorbed when allowed to remain in a wound after the closure of the incision.

The hemostatic property of oxycellulose is dependent upon the formation of an artificial clot by cellulosic acid. Although cellulosic acid exhibits a marked affinity for hemoglobin, it does not enter into the physiologic process of clotting.

Oxidized cellulose is a very valuable hemostatic agent in surgery where the control of bleeding is difficult to achieve by suturing or ligation. It is not advisable to use oxidized cellulose as a surface surgical dressing except for the purpose of hemorrhage control. Cellulosic acid applied to a surface wound inhibits epithelization.

**Surgical, oxidized, regenerated cellulose.** Oxidized regenerated cellulose is prepared from alpha-cellulose, derived from a highly purified form of cotton linters. The alpha-cellulose is converted, in an alkaline organic solvent, to a viscose. This is then forced through spinerettes into a coagulating bath, where the material is regenerated in the form of pure uniform filaments, while at the same time undesirable by-products are separated and removed. The filaments of the pure regenerated cellulose are then spun into threads and knitted into gauze, or made into carded fiber pads similar in appearance to absorbent cotton.

The product is supplied in gauze-like strips of different sizes similar in appearance to absorbent cotton. The 3 properties of the product that mark it as a valuable addition to the hemostatic agents are: (1) dependable hemostatic activity, (2) absorbability without tissue irritation, and (3) stability.

**Thrombin, U.S.P.** "Thrombin is a sterile protein substance prepared from prothrombin of mammalian origin through interaction with added thromboplastin in the presence of calcium. It is capable of accelerating the clotting time of blood. The prothrombin is usually of human or bovine origin. Thrombin complies with the official potency test and other requirements of the National Institutes of Health."

Thrombin is employed as a hemostatic agent by topical application. Its principal use is in the control of capillary bleeding during surgical procedures. Thrombin may be applied locally as a dry powder or dissolved in normal saline solution. The potency is expressed in units of clotting activity. Usually from 1000 to 5000 units are employed.

### Estrogens in Control of Hemorrhage

There have been numerous reports on the value of estrogens in the control of hemorrhage. Their value in the control of postoperative bleeding appears to be established.

Fox (1960) critically evaluated the effect of estrogens in hemorrhage after tonsillectomy and adenoidectomy in 503 patients. He used 20 mg. of conjugated estrogens (equine) "Premarin" intravenously. There was a definite diminution in bleeding in the treated patients. There were no adverse effects.

Evidence that estrogens affect the clotting mechanism of blood is not convincing. Poliwoda (1962) used estriol succinate to check hemorrhage in patients on anticoagulant therapy. A study of the mechanism of action revealed that the interfibrillar ground substance of the small vessels and capillaries undergoes a generalized change that results in the sealing of the wall. The thrombocyte count returns to normal levels, in some cases within a period of 5 to 8 weeks. No effect on the plasma clotting factors could be detected.

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# 45

# *The Response of the Hematopoietic System to Drugs*

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In the preceding chapter it was observed that pharmacologic agents can markedly influence the clotting time of blood. Furthermore, the management of the clotting time of blood with drugs was found to be of clinical importance. In this chapter we shall give attention to the hematopoietic system. Our first consideration will be the use of drugs in the treatment of various anemias. The anemias discussed in this chapter are primarily either hypochromic microcytic (iron deficiency) or macrocytic megaloblastic (vitamin deficiency).

**Iron metabolism.** Iron is present in every cell of the body. The amount of iron in the human body varies between 3 and 5 gm. Approximately ⅔ of the total iron of the body is present in the blood. Iron is the keystone of the structure of the hemoglobin molecule. The vast, vital process of respiration must ultimately funnel through a few grams of iron. Approximately 90 per cent of the iron content of blood is there as a portion of the molecule of hemoglobin. Iron is present in the blood in 3 forms: (1) hemoglobin iron, (2) plasma iron from 50 to 180 $\mu$g./100 ml. and (3) iron which is easily separated from hemoglobin by diluted mineral acids. This last-mentioned iron fraction is probably loosely bound with hemoglobin; it is likely non-hemoglobin iron. Plasma iron is bound to $\beta_1$-globulin, *transferrin*, or *siderophilin*. The iron-binding $\beta_1$-globulin has been crystallized. Human plasma contains about 2.4 gm./L. of the globulin, and each gram binds 1.25 mg. of iron. The $\beta_1$-globulin has a molecular weight of about 90,000. It is of interest that the serum of the normal adult is about ⅓ saturated with iron. In iron-deficiency anemia this value diminishes to about 10 per cent. The serum iron level plus the unsaturated or *latent iron-binding capacity* (LIBC) is equivalent to the total transferring or iron-binding capacity (TIBC). It is possible by means of radioactive iron to determine the rate that iron atoms leave the plasma and are replaced by new, incoming iron atoms. In normal persons approximately 90 per cent of the iron leaving the plasma is deposited in the bone marrow. Thus the plasma iron turnover refers mainly to the amount of iron furnished to the hematopoietic organ.

In *hemochromatosis* and *transfusion hemosiderosis* $\beta_1$-globulin becomes 100 per cent saturated. The administration of excessive amounts of iron salts may produce tissue changes which progress from hemosiderosis of the liver to portal fibrosis. These changes were demonstrated in anemic and nonanemic rabbits by massive intravenous injections of colloidal iron.

Iron is absorbed from the gastrointestinal tract, primarily from the upper portion of the small intestine. It is absorbed by the epithelial cells of the intestinal mucosa and passes from the intestinal capillaries into the blood.

The fate of iron in the mucosal cell involves a complicated biochemical process. Enzymes first oxidize the iron to the ferric state, namely, a ferric hydroxide phosphate complex. This insoluble compound within the mucosal cell forms micelles. These unite with a protein called *apoferritin* to form a complex designated as *ferritin*. Ferritin is a convenient storage form for iron. When apoferritin is saturated with iron the mucosal cell cannot assimilate more iron, and a mucosal barrier is established. The iron in ferritin is trivalent. The ferrous iron in the mucosal cells is in equilibrium with the ferritin ($Fe^{+++}$) in these cells and with the plasma iron ($Fe^{++}$) of the bloodstream. The quantity of $Fe^{++}$ which will be absorbed by the cell is dependent upon the level of $Fe^{++}$ in the cell and indirectly upon the ferritin concentration. From the mucosal cells $Fe^{++}$ passes into the blood. The amount which enters the blood is dependent upon the redox level of the mucosal cells and this in turn is related to the oxygen tension of the blood. Only $Fe^{++}$ passes into the blood.

Ferritin releases iron into the circulating blood. Iron is transported in the ferric state combined with $CO_2$ and attached to one of the $\beta$-globulins known as *siderophilin* or *transferrin*. In this form it may be carried to the tissues to be stored as ferritin. This is exchangeable iron. That which is utilized in the cytochrome systems is not exchangeable. The transfer of iron from the intestinal lumen to transferrin is outlined in figure 45-1.

The storage depots for iron are the nuclei of cells, the bone marrow, spleen and liver. Barer and Fowler (1940) in their studies of the iron requirements needed in the daily diet, found that from 4 to 7 mg. of the metal daily soon produced a negative iron balance. From 12 to 15 mg. of iron daily produced positive iron balances. They found that achlorhydria and hypochlorhydria materially retarded the retention of dietary iron, and therefore such individuals required a larger intake of iron to maintain a positive balance. A usual adequate diet in temperate climates will supply from 10 to 40 mg. of the metal daily (Demulder, 1958).

Excessive quantities of iron above the requirements of the body tissues are excreted through the wall of the colon and appear in the feces. This, however, does not account for all the iron excretion. Barer and Fowler (1937) found that the urinary excretion of iron from 100 men ranged from 0.09 to 1.29 mg. per day. The average was 0.395 mg. The urinary excretion of iron by women is 25 per cent greater than that of men. Patients with idiopathic hypochromic anemia excreted a larger quantity of iron than other individuals. It is of interest that the urinary excretion of iron is rather constant in the same individual regardless of his iron intake.

The urinary and gastrointestinal excretion of iron does not account for the disposition of the daily iron intake. This concept of iron excretion conceives of the human organism as a tight compartment with regard to iron. It implies that little or no exogenous iron is absorbed in the closed compartment other than that necessary to replace blood loss. Mitchell and Hamilton (1949) observed that human perspiration contained a considerable quantity of iron. Under ordinary conditions 0.3 mg./hour of iron is excreted in the sweat. This is about 13 per cent of the dietary intake. Indeed these studies demonstrate that an important pathway of iron excretion is through the perspiration. Adams *et al.* (1950) hold the view that the dermal loss of iron is associated more with desquamation than it is with sweating. The combined phenomena account for the disappearance of a considerable quantity of iron.

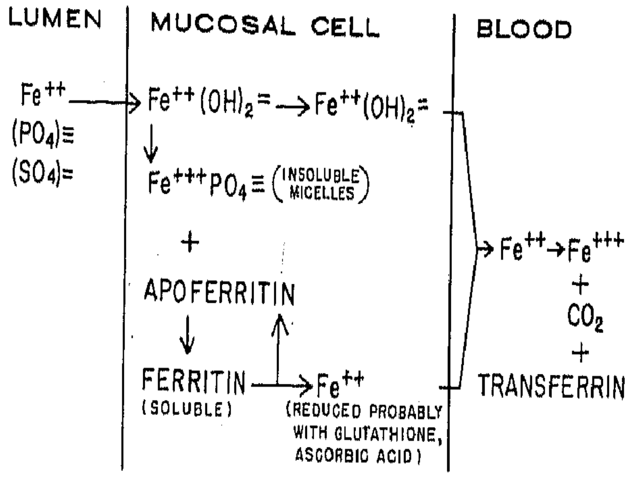


FIG. 45-1. Absorption and transport of iron

It appears that the absorption of iron rather than the excretion of iron determines the iron content of the tissues. For example, by the use of radioactive iron Hahn *et al.* (1943) showed that anemic dogs absorbed much more of the metal from the gastrointestinal tract than normal animals. A normal dog absorbs between 1.6 and 6 per cent of radioactive iron given orally. In states of iron deficiency the degree of absorption may reach 66 per cent (Stewart, 1953). The absorption of iron from the tract is increased by chlorophyll, bile pigments, calcium salts, and high dietary ascorbic acid levels. Its absorption is retarded by gastric hypoacidity, excessive mucus in the intestine, inflammation, disease and sterilization of the gastrointestinal tract (as with tetracyclines, page 111). In addition, malabsorption syndromes associated with sprue, chronic diarrhea, and ulcer therapy will decrease the amount of iron absorbed.

The body tissues have the capacity to re-utilize iron which has served its initial function. For example, when the erythrocytes have completed their life cycle, the iron may be re-utilized through the complex mechanism of iron transfer and storage. In this manner a low absorption of iron may be compensated for by the re-utilization of the iron which has passed through a catabolic cycle. An outline of iron metabolism is shown in figure 45-2.

**Origin of hemoglobin.** Hemoglobin is formed in red bone marrow. The total available tissue for hematopoietic activity is estimated at 1400 gm. It is capable of producing several times its own weight of red cells every 2 or 3 weeks. It is estimated that each day $10^{12}$ red cells are produced and during a life's span approximately 1 ton of red cells is sent into the blood stream.

Hemoglobin is a conjugated protein which consists of an iron-containing pigment combined with a protein of the *histone* class known as *globin*. The iron-bearing portion of the hemoglobin molecule is a *porphyrin*. The porphyrins are widely distributed in the plant and animal kingdoms. Chemically they consist of the union of 4 pyrrole rings. Hemoglobin is a metallo porphyrin; as previously stated the metallic atom is iron in the ferrous state $Fe^{++}$. This porphyrin is designated as iron protoporphyrin or *heme*. It was assumed formerly that heme was synthesized in the bone marrow or possibly in the spleen and liver. There was little convincing evidence. Walsh *et al.* (1949), using an *in vitro* study with radioactive iron as $Fe^{59}$ or $Fe^{55}$, produced cogent evidence to show that the synthesis of heme occurs in the immature erythrocyte itself. Folic acid or liver extract increased the rate of heme synthesis by the erythrocyte which was demonstrated by an increased iron uptake. Heme is a constituent also

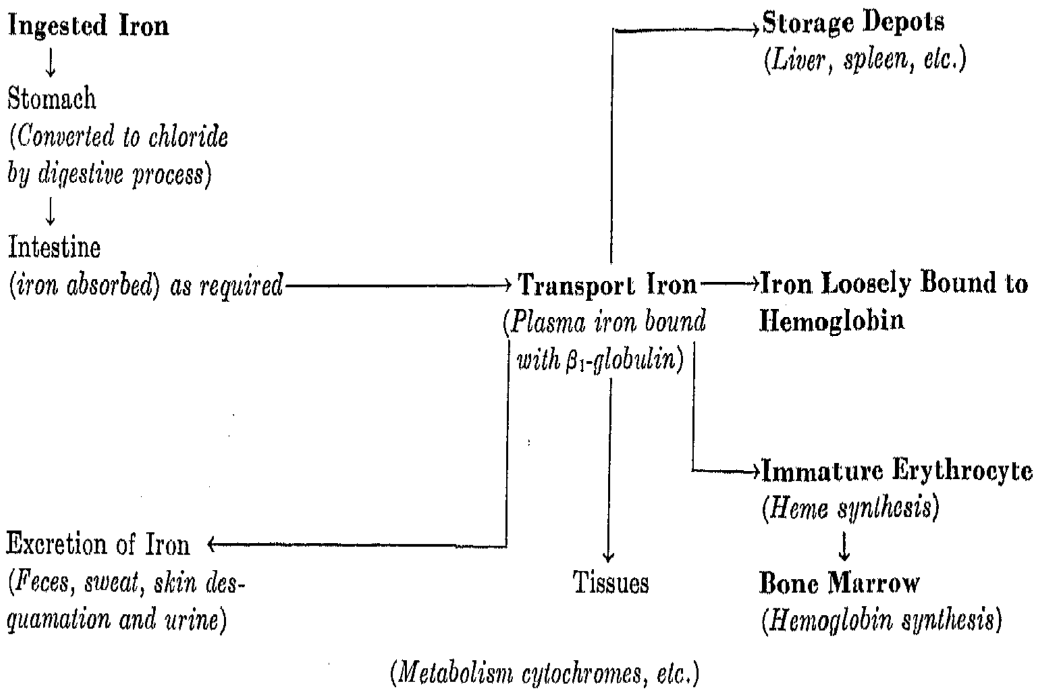

Ingested Iron
Stomach
(Converted to chloride by digestive process)
Intestine
(iron absorbed) as required
Transport Iron
(Plasma iron bound with β1-globulin)
Storage Depots
(Liver, spleen, etc.)
Iron Loosely Bound to Hemoglobin
Immature Erythrocyte
(Heme synthesis)
Bone Marrow
(Hemoglobin synthesis)
Excretion of Iron
(Feces, sweat, skin desquamation and urine)
Tissues
(Metabolism cytochromes, etc.)

Fig. 45-2. Schematic outline of iron metabolism

of other systems concerned with oxygen exchange, such as the cytochrome system.

It appears therefore that to provide the building stones to the marrow for hemoglobin synthesis it is essential to have:

1. Available iron;
2. Pyrrole groups necessary for porphyrin synthesis;
3. Amino acids necessary for globin synthesis.

The anemias which result from a deficiency in factors necessary for hemoglobin formation or through the loss of blood may be classified as *hypochromic microcytic anemias.* They are treated by means of an adequate diet plus the administration of iron salts. The basic defect causing the anemia must be corrected if possible. In these types of anemia, frequently referred to as *iron-deficiency anemias*, medication with iron salts is the standard method of treatment.

**Choice of an iron preparation.** Iron is an old medicine. It was known as a medicine to the ancient Greeks. According to Greek legend, Mars, the god of war, endowed the metal with strength. Water in which old swords were allowed to rust was administered to treat the feeling of weakness. The English physician Sydenham, toward the end of the seventeenth century, used iron in the treatment of *chlorosis.* In the beginning of the eighteenth century Lemery and Goeffy discovered the presence of iron in the ash of blood. In 1832 Pierre Blaud of France provided an impetus to iron therapy in his use of ferrous carbonate in the treatment of chlorosis. He emphasized adequate dosage levels and the pills of ferrous carbonate bearing the name of Blaud received worldwide acceptance. Today the only rational use of iron therapy is in the treatment of iron-deficient microcytic anemia.

There are abundant forms in which it has been administered, and the national pharmacopeias recognize a large number of iron salts. In the main the iron preparations used in the treatment of iron-deficiency anemia can be classified as follows:

1. Reduced iron (the finely divided metal)
2. Soluble ferrous salts
   a. Ferrous sulfate
   b. Ferrous gluconate, etc.
   c. Iron chelate compounds
3. Soluble ferric salts of organic acids
   a. Ferric ammonium citrate
   b. Soluble ferric phosphate with sodium citrate
4. Parenteral iron preparations.
   a. Saccharated iron oxide (Feojectin)
   b. Iron-dextran complex (Imferon)

Moore *et al.* (1939) showed that serum iron absorption curves are higher following the administration of ferrous salts than of ferric salts. Bergeim and Kirch (1949) showed the necessity of hydrochloric acid in the stomach for the absorption of iron from food complexes. Also, they emphasize the value of ascorbic acid in the stomach for the reduction of iron to the ferrous state for optimal absorption. Reducing sulfhydryl groups present in the stomach during digestion also contribute to the reduction of $Fe^{+++}$ to $Fe^{++}$ and promote absorption. Ferric salts of inorganic acids are astringent to mucous membranes and are more irritating. These salts have been largely discarded in the treatment of anemia.

Reduced iron is official in many pharmacopeias. The iron is very finely divided. Its absorption depends on the solution of the metal in gastric acid, producing ferrous chloride. Its content of pure iron is greater than 90 per cent. The absorption of reduced iron as soluble iron salts is surprisingly efficient. Its use is declining, however. It is of interest that finely divided metallic iron, in particles too small to be measured in microns, was shown to be rapidly absorbed by the buccal mucosa when placed under the tongue. It has been demonstrated that iron crystals in rod shape that were 50 to 500 Å in diameter could rapidly increase the iron content of the blood when placed under the tongue. This is an interesting phenomenon, the passing of a metallic element into the blood by sublingual administration.

Of the many soluble ferrous salts available, ferrous sulfate is the compound of choice. It is available in capsules and tablets and is readily soluble. One does not need to depend upon gastric acid for the solubilizing of the iron salt. The crystallized salt is deprived of most of its water of hydration, which increases its iron content, and the exsiccated ferrous sulfate is used medicinally. Some individuals do not tolerate ferrous sulfate well, and in these patients ferrous gluconate or ferrous glycinate is preferred. Numerous cases of poisoning from overdosage with ferrous sulfate have appeared in the literature. None have appeared owing to toxicity from ferrous gluconate (Hoppe *et al.*, 1955). They showed in laboratory animals that ferrous gluconate is less irritating and less toxic than ferrous sulfate when considered either from the standpoint of weight of salt administered or of their respective iron contents.

Ferric ammonium citrate is a so-called *scale salt* of iron. It is a mixture of iron citrate and ammonium citrate which is quite soluble in water. No special advantage seems to accrue by combining the ferrous iron with ascorbic acid, gluconic acid, glycine, fumaric acid, or other organic acids to form ferrous salts. It appears that simple inorganic salts are the most effective and ferrous sulfate is the salt of choice.

The daily dosage of any iron salt selected in the treatment of iron-deficiency anemia is dependent upon its content of iron and the efficiency with which it is absorbed.

Considering the efficiency of each one of the iron salts in supplying iron that is utilizable, the value of reduced iron is slightly less than 1 per cent. Ferric ammonium citrate provides only 2 per cent of utilizable iron. On the other hand, ferrous sulfate provides approximately 20 per cent of utilizable iron. Therefore, as a source of available iron this salt is preferred.

**Hemoglobin response to iron medication.** In the treatment of iron-deficiency anemias it is generally conceded that an increase of 1 per cent daily in hemoglobin is a satisfactory response. This response is optimal, and this rate of hemoglobin increase occurs in the beginning of the iron therapy. It diminishes as the percentage of hemoglobin returns toward normal. It is estimated that the utilization of 25 mg. of iron daily will provide for a 1 per cent increase of hemoglobin. One gram of ferrous sulfate provides 200 mg. of iron. On the assumption of a 15 to 20 per cent utilization, this amount of the iron salt will provide 30 to 40 mg. of utilizable iron. This is more than adequate to provide for the 1 per cent daily increase in hemoglobin. Certainly from the standpoint of the patient the more efficient is the utilization of iron, the more satisfactory is the therapy. It is impossible to say just how much iron is adequate. It varies tremendously with the individual patient.

The efficiency of iron absorption from the gastrointestinal tract often bears an inverse correlation to the dose. For example, if 1000 mg. of iron salt is administered and the absorption is 10 per cent, 100 mg. of the salt is available. If the dose is reduced to 100 mg. the degree of absorption may increase to 30 per cent. This would make available, however, only 30 mg. of the iron salt. Therefore, in practice large dosage schedules are indicated provided they are well tolerated by the patient. The medication should not be stopped as soon as the hemoglobin levels are normal, owing to the fact that an iron deficiency in the tissues may still prevail.

The utilization of iron with a typical hemoglobin increase is shown in figure 45-3.

When ferrous sulfate is used in iron-deficiency anemia, the initial daily dose is usually 0.6 gm. given in 2 tablets when the stomach is full. This usually prevents gastric irritation. As the patient becomes accustomed to the therapy the dose may

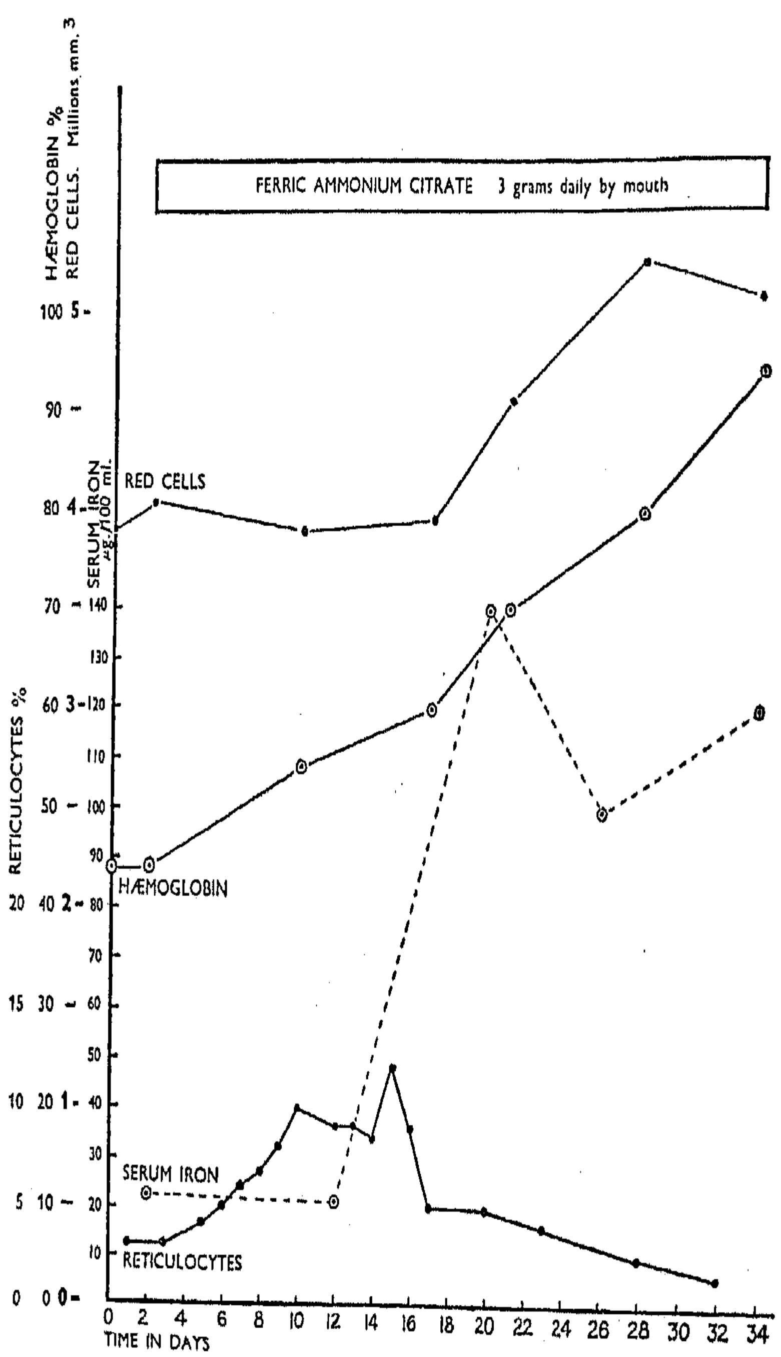


FIG. 45-3. The effect of oral administration of iron on the blood of a female patient aged 74 with an iron-deficiency anemia. (From *Textbook of Physiology and Biochemistry*, 2nd Ed. Bell, Davidson and Scarborough, The Williams & Wilkins Company, Baltimore, 1953.)

be increased to 1 or 1.2 gm. daily. An adequate diet of meat, fruit and vegetables is desirable. Failure to respond to oral iron medication, necessitating the parenteral administration of iron salts, is seldom encountered.

The quantities of iron used in therapy according to the foregoing dosage schedules do not alter significantly the phosphorus, calcium, or nitrogen balances.

**The toxicity of ferrous sulfate.** The toxicity of ferrous sulfate has been studied in several cases of accidental poisoning with sugar-coated pills in children. Smith (1952) studied the tissues of a 21-month-old child who was fatally poisoned by the ingestion of ferrous sulfate pills. The mucosa of the stomach was congested and necrotic, and many hemorrhagic areas were present. There was a high intravenous concentration of iron. Smith discusses the cause of the child's death and believes that it can be related to ferritin. He postulates the possibility of the depressor response produced by excessive amounts of ferritin as being responsible for the shock-like syndrome of ferrous sulfate poisoning. Ferritin has been shown by Shorr *et al.* (1945) to be a factor in producing a shock-like syndrome. Ferritin has been shown to inhibit the vasoconstricting activity of epinephrine, causing a fall in blood pressure. The protein also stimulates the neurohypophysis to secrete the antidiuretic hormone and thus elicits an antidiuretic effect (Mazur *et al.*, 1958).

The absorption of iron from the gastrointestinal tract is increased by an excess of iron or an insufficiency of phosphate in the tract. In case of poisoning with massive amounts of ferrous sulfate, the excess of iron destroys the *mucosal barrier*, and excessive amounts will enter the mucosal cells. This may escape into the circulation. Further, the excessive serum iron may be converted into ferritin in the liver, spleen, and marrow, and ultimately find its way into the circulation. Thus shock, which is an important characteristic of iron poisoning, might be initiated and maintained. Smith believes that the shock-like state is the cause of death. This work sheds light on the hitherto obscure mechanism of iron poisoning and correlates well with the dynamics of iron metabolism.

Most cases of iron salt poisoning occur among children. Clark *et al.* (1954) reviewed 26 cases of iron poisoning reported since 1947; about half of them were fatal. He considers that the intoxication occurs in 3 critical phases. The first is an early acute phase of shock that supervenes within a few hours after the ingestion of the iron; the second recurrent phase appears in 20 to 48 hours after the poisoning; and occasionally, a third phase of gastric scarring and contracture with pyloric obstruction may appear in about a month after the initial episode. Cann and Verhulst (1960) report death within 5 hours after ingestion of ferrous sulfate. The committee on toxicology of the American Medical Association recommends that ferrous sulfate and similarly hazardous iron salts be labeled with a caution statement with special reference to children.

The shock-like state is treated by the usual supportive measures. Methionine is recommended on the basis that iron reacts with sulfhydryl groups in essential enzymes, and methionine will compete for the iron atoms. There appears to be no agreement concerning the value of BAL in iron poisoning. The consensus indicates that it is ineffective if given after 12 hours. Newer derivatives of ethylenediaminetetracetic acid show some promise in the removal of iron, both in acute and chronic poisoning. Desferrioxamine has been used successfully in the treatment of ferrous gluconate poisoning (Henderson *et al.*, 1963). These substances are still experimental, however. D-Penicillamine has been shown to increase urinary iron excretion, but its utility in iron poisoning remains to be elucidated (Done, 1961).

Buttner and Muhler (1959) demonstrated that the feeding of ferrous sulfate to rats significantly increased the iron content of the liver. However, when sodium phosphate was administered simultaneously, a significant reduction in the iron content of the liver occurred; this indicates a diminution in iron absorption and utilization in the presence of soluble phosphates.

**Iron chelates.** Iron salts have a low dissociation constant at the hydrogen ion concentration present in the intestinal tract from which they are absorbed. There is the possibility that some chelating agent is secreted by the mucosal cells to chelate the iron and promote its absorption. Such a mechanism would accelerate the absorption of iron over the diffusion of the low concentration of $Fe^{++}$ into the mucosal cells. Although the presence of such chelating agents has not been demonstrated in animals, their presence in plants appears to be established.

Iron salts can be readily chelated for medication, and certain iron chelates have already taken their place among the available iron preparations in medicine. Pomeranze and Gadek (1957) studied an α-aminoacetic ferrous sulfate complex (Ferronord) in the treatment of iron deficiency anemias. The preparation was readily tolerated in patients who did not tolerate other iron preparations. The reticulocytosis response was prompt, and there appeared to be no side effects even when the tablets were administered between meals. Each tablet of Ferronord contains 40 mg. of ferrous iron, and the recommended dose is 2 tablets 3 times daily between meals. In 54 patients with an average hemoglobin of 9 gm./100 ml., after 25 days of medication with the foregoing dosage level the average hemoglobin had increased to 14.5 gm./100 ml.

Another iron chelate preparation is iron choline citrate (Ferrolip). This iron chelate is soluble, one gm. in 0.2 ml. of water, and retains its chelated iron atom at a pH of 10.2 in the presence of such iron precipitants as protein, phosphates, and carbonates. Animal experiments showed that iron in chelate formation was less toxic than an equivalent amount of iron in the form of ferrous sulfate or gluconate. Franklin *et al.* (1958) used this product in 131 patients in doses of 120 to 240 mg. daily for a total of 3303 treatment days. The hematinic response was adequate and only 6 patients manifested any gastrointestinal disturbance. In those, the symptoms were transient and medication was continued.

Evidence indicates that chelated iron preparations are useful hematinics, and also they appear to offer some advantage over ferrous salts where the latter are not well tolerated or readily absorbed.

**Parenteral iron therapy.** There are relatively few indications for parenteral iron therapy. Ulcerative colitis, other gastrointestinal disturbances, sensitivity to oral iron therapy, and failure to respond to oral iron medication are conditions in which parenteral iron therapy is indicated. For this purpose *saccharated iron oxide* appears to be useful. The product is available under the name "Feojectin" which contains in colloidal solution an amount of iron oxide equivalent to 20 mg. of elementary iron in each milliliter. The doses range from 40 mg. to 60 mg. of iron intravenously the first day; 100 mg. is given each subsequent day until a satisfactory hemoglobin response is achieved. Most patients experience a satisfactory response when a total dosage of 700 to 2000 mg. are given (Brown *et al.*, 1950). Excessively large doses may produce hemochromatosis.

Evans and Waltman (1953) caution against the rapid injection of the drug. With slow and careful administration, as a rule no untoward effects are encountered. Rapid injection may give rise to pain at the site of injection, flushing, dyspnea, lumbar pain, and syncope.

Another preparation of this character is *dextriferron* (*Atrafer*). It is a colloidal solution of ferric hydroxide in complex with partially hydrolyzed dextrin. Dextriferron contains the equivalent of 20 mg./ml. of iron, has a pH of 7.6, and is stable for periods of 2 years. The same precautions in administration and extent of use prevail with dextriferron as discussed under saccharated iron oxide. From 1.5 to 5 ml. is the daily dose intravenously.

Another parenteral iron preparation is an *iron-dextran complex* (Imferon) containing 50 mg. of iron in 1 ml. This iron preparation is administered intramuscularly and enjoys a high margin of safety. Wallerstein and Hoag (1957) used the product in the treatment of iron-deficiency anemia in children at a dosage level of 50 to 100 mg. of iron daily. The hematinic response was prompt and satisfactory. The hemoglobin level generally reached 11 gm./100 ml. in 3 weeks of treatment. They found the preparation satisfactory and safe. At least 1 gm. of iron can be given to infants with impunity in this dextran complex.

Haddow and Horning (1960) observed that massive doses of Imferon injected repeatedly into the same site over long periods of time ultimately induced sarcomata at the injection site in certain strains of mice and rats. This did not prevail in the rabbit or guinea pig. For this reason the preparation was withdrawn from the market by the manufacturer in America, pending further investigation. There is no evidence available to indicate that Imferon is carcinogenic in man, and more than 12 million doses have been administered clinically. It is now available again for clinical use.

Pritchard (1961) compared the response to oral and parenteral iron therapy in patients with severe anemia owing to chronic hemorrhage. Iron-dextran was given intramuscularly and ferrous gluconate orally in adequate dosage levels. After 19 days the mean hemoglobin concentration increased 5 gm./100 ml. with parenteral iron and 4.9 gm./100 ml. in 24 days with oral iron therapy. With parenteral iron the rate of hemoglobin production averaged 3 times normal and with oral iron, 2.4 times normal. He concluded that little reason existed in these cases for the use of parenteral iron. It is our opinion that this conclusion holds for the vast majority of iron deficiency anemia patients.

**Adjuncts to iron therapy.** Although iron is the keystone of the molecule of hemoglobin, the other building materials must also be provided. The best provision for these is an adequate diet, and as a rule that plus the iron therapy will suffice.

The porphyrin portion of the hemoglobin molecule is present in the great majority of foodstuffs. The globin portion of the hemoglobin molecule is available from most meats. Whipple (1928) observed that meat protein is efficiently utilized for hemoglobin synthesis. One hundred grams fed will produce from 30 to 40 gm. of blood pigment. He found that the globin portion of the hemoglobin molecule was of much greater dietary significance in hemoglobin formation than the porphyrin. Globin appears to be an important limiting factor in the synthesis. For example, a diet low in protein but adequate in iron is an anemia-producing diet. Illustrative of this fact is the observation of Whipple (1928) on the efficacy of certain materials for hemoglobin production (table 45-1).

It is obvious from the data in this table that protein, especially that found in liver, is necessary for hemoglobin formation.

TABLE 45-1

*Hemoglobin Production and Diet*

(Whipple, 1928)

| Diet Grams Daily | Hemoglobin Production in 2 Weeks |
|---|---|
| | *gm.* |
| Bread 400 | 3 |
| Milk 450, bread 400 | 3 |
| Beef muscle 250, bread 300 | 17 |
| Eggs 150, bread 300 | 45 |
| Kidney 250, bread 300 | 70 |
| Chicken liver 250, bread 300 | 80 |
| Beef liver 300, bread 300 | 80 |
| Beef liver 450 | 95 |

These data pose the question of the value of liver in the treatment of iron-deficiency anemias. Castle (1936) states, "We have never seen a case of hypochromic anemia that would not respond to iron but would respond to liver or some liver fraction." Later, however, they arrived at the opinion that in rare cases where iron is insufficient liver may help. Strauss (1936) recognized the possible value of the use of 200 gm. of liver daily in cases of hypochromic anemia, especially when chronic blood loss is the dominant etiologic factor. Fowler and Barer (1939) arrived at the opinion that liver extract is not necessary to supplement iron in the treatment of anemia. This of course holds when the patient receives an adequate diet containing the available protein for globin synthesis.

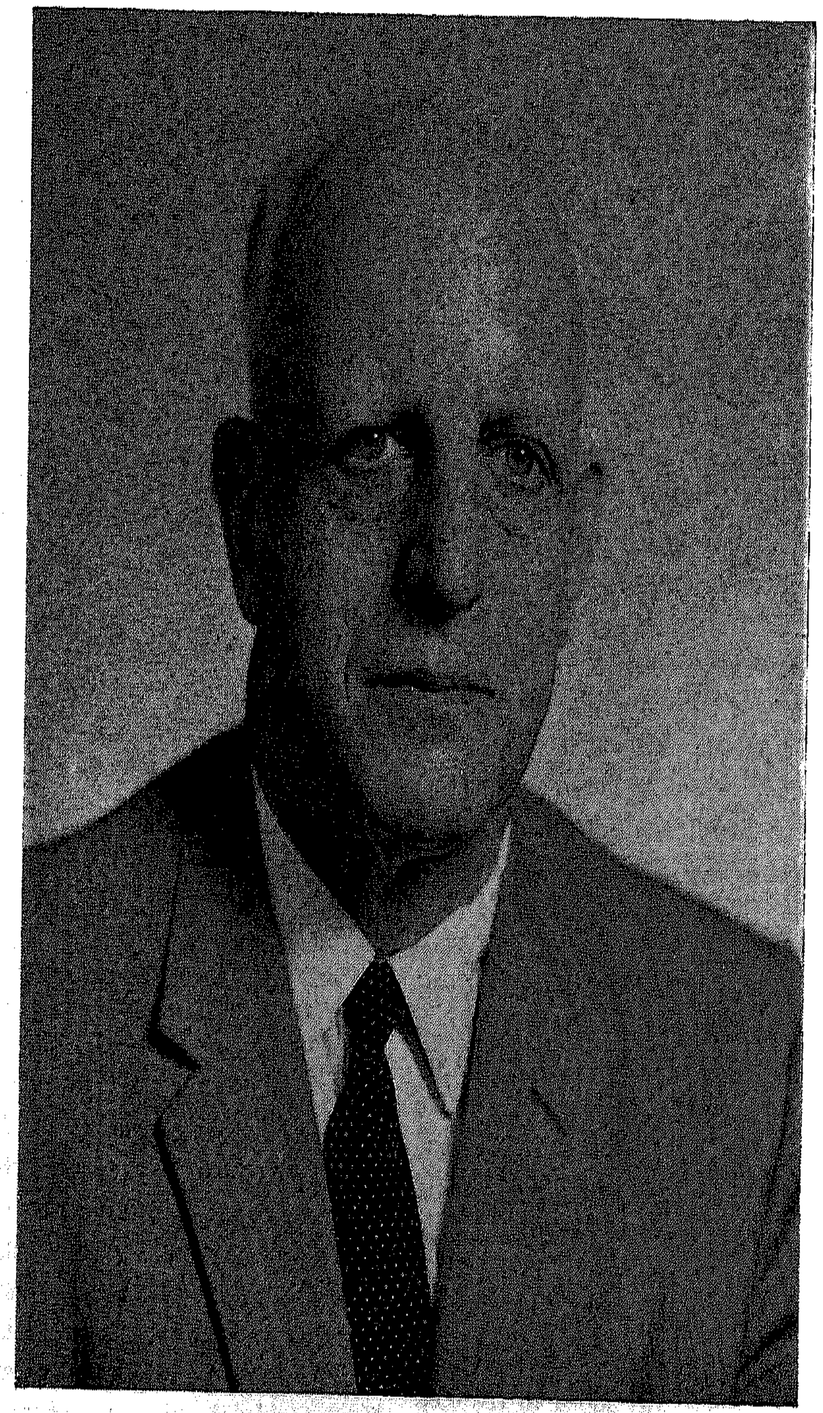
Waddell *et al.* (1929) found that rats rendered anemic by milk feeding did not regenerate hemoglobin when iron alone was added to the diet. When, however, the iron was supplemented by traces of copper salts, hemoglobin regeneration occurred. Manganese also exerts this catalytic effect upon iron but to a lesser degree than does copper. The liver is the depot of copper storage. Lahey *et al.* (1953) confirmed the observation that the blood of women contains more copper than that of men. They determined that the whole blood of males contained 96 ± 13 µg. of copper/100 ml.; that of females contained 100 ± 11 µg./100 ml. The changes of copper level are very slight from day to day. Heilmeyer *et al.* (1951) made copper determinations on the blood of 3000 patients suffering with iron-deficiency anemia and never found an abnormal low level. However, there are rare cases reported in which a copper supplement to iron therapy appeared to be useful (Cartwright, 1947). An adequate diet provides ample copper to catalyze the action of iron. The addition of copper to iron therapy in iron-deficiency anemias has been shown to be of no value except in rare cases.

Cobalt salts elicit a marked reticulocyte response owing to an effect other than the fact that a cobalt atom is a constituent of the molecule of vitamin $B_{12}$. The action of cobalt upon the hematopoietic system is blocked by compounds containing sulfhydryl groups. The mechanism of this action of the cobalt ion is not understood. Rovati (1954) showed that the administration of cobalt salts constantly lowers the serum-iron concentration and increases the erythrocyte count, producing a polycythemia. Cobalt appears to have no place in the treatment of iron deficiency anemias. Without a sufficient amount of iron and copper, cobalt salts are ineffective.

**The mechanism of action of iron in anemia.** In individuals with a normal red cell count transferrin is approximately ⅛ saturated with iron. In iron-deficiency anemia the serum iron level is low, but the capacity of transferrin to accept iron is augmented. When iron is made available it is absorbed and utilized. Iron-deficiency anemia results frequently from hemorrhage. Other contributing factors are dietary deficiency and hypochlorhydria. In the latter case iron is not efficiently absorbed. Therefore the treatment of iron-deficiency anemia is mainly one of supplying a deficiency. Iron as such has no stimulating effect on hemoglobin formation and hence is of no value unless the anemia is due to a deficiency of available iron. Iron provides the "keystone of the arch" for the hemoglobin molecule.

## PERNICIOUS ANEMIA

The first case of pernicious anemia was described by J. S. Combe of Edinburgh in 1822. The condition was recognized as a disease entity by Addison in 1850. The malady is often referred to as *Addisonian anemia* or *idiopathic anemia.* Frank A. Evans, in his interesting volume on the subject written in 1926, opens his discussion with the following cogent statement, "Progressive pernicious anemia is a term used to designate a most interesting and complex condition, so-



WILLIAM B. CASTLE

*Originator of the Castle hypothesis of the etiology of pernicious anemia*

"Pernicious anemia has been a hard taskmaster but a great teacher. The results of the curiosity aroused in her students show that whatever may be the future of clinical investigation, the study of this disease has, up to the present, provided insight into matters not previously suspected to exist."

called because it is invariably fatal, and clinically exhibits anemia as one of its outstanding features." Shortly after the appearance of this book the old "wine of despair" was to be placed in "new bottles of hope," for the value of liver in the control of the disease was discovered by Minot and Murphy in 1926.

**Nature of pernicious anemia.** The onset of pernicious anemia is generally gradual, the most common early complaint being that of chronic fatigue. *Glossitis* is a frequent early symptom, and the tongue is seldom coated. These symptoms are followed by *anorexia, nausea, vomiting,* and *diarrhea. Symmetrical paresthesias* of the hands and feet may occur as the spinal cord becomes involved.

The gastric manifestation of pernicious anemia is usually constant. There exists a true achlorhydria in which the acid-producing cells of the stomach fail to respond to histamine injections (page 921).

The blood picture of pernicious anemia is similar to that of *macrocytic nutritional anemia.* In the latter, however, the achlorhydria is not a factor. The blood picture of pernicious anemia shows evidence of diminished bone marrow activity. The red cell count is usually below 2 million. The corpuscular volume is large, and the color index is generally greater than unity. White blood cells and platelets are reduced in number also. The bone marrow is increased in quantity and shows marked hyperplasia of megaloblasts.

**Etiology of pernicious anemia.** Essentially pernicious anemia is a deficiency disease. It is due to a biochemical lesion which interferes with the factor *essential for the maturation of the red cells.* The megaloblasts fail to mature. The factor or principle necessary for the maturation of the erythrocytes is called the *antipernicious anemia principle* or the liver factor.

According to Castle's hypothesis an *extrinsic factor* is present in beef muscle, milk, eggs, and other foods, which is acted upon by an *intrinsic factor* secreted by the stomach to form the antipernicious anemia principle. The extrinsic factor is extractable from meat with 70 to 80 per cent alcohol. The antipernicious anemia factor thus formed by the union of the extrinsic and intrinsic factors, responsible for normal hematopoiesis, is stored in the liver.

The antipernicious anemia principle released from the liver functions in the bone marrow, enabling the embryonic hematopoietic tissue maturation to proceed in a normal manner. The megaloblastic stage proceeds to the normoblastic stage in the development of the red cell.

The patient with pernicious anemia is incapable of producing adequate quantities of the antipernicious anemia principle. Treatment is based upon replacement therapy, *i.e.,* supplying the antipernicious anemia principle.

**Historical development of liver therapy.** Based upon the classic researches of Whipple and his associates in hemoglobin regeneration produced by liver, Minot and Murphy (1926) fed large amounts of whole liver to 45 patients with pernicious anemia. The improvement was striking. The feeding of several hundred grams of liver daily was a difficult regimen. It was soon observed that the antipernicious anemia principle of mammalian liver could be extracted and concentrated. The active substance is indeed only a very small fraction of the weight of whole liver.

Cohn *et al.* (1928) separated whole liver into its soluble and insoluble fractions. The insoluble portion was inert when fed to patients with pernicious anemia. The soluble fraction was purified further by the removal of coagulable proteins. The substance was further purified by precipitation with alcohol. This substance, called "fraction G," contained a high concentration of the antipernicious anemia principle.

Today extracts of liver are available in which a few grams of powder represent the antipernicious anemia principle of a half-pound of liver.

It was demonstrated by Castle and Townsend (1929) that beef muscle, inert in the treatment of pernicious anemia, could be activated by treatment with normal gastric juice. This procedure brings together the extrinsic and intrinsic factors previously mentioned. Stomach preparations obtained in this manner have been used in the treatment of pernicious anemia. The bulk of the extract is large, and much difficulty is experienced on the part of the patient in taking the medicament 2 or 3 times daily.

Walden and Clowes (1932) found that fresh liver extracts when mixed with small quantities of freshly ground stomach tissue extracts were more active therapeutically than either product individually. Liver-stomach preparations are of small bulk and are used in the treatment of pernicious anemia.

Liver extracts are available which are suitable for intramuscular medication. This represents a great advance in the therapy of pernicious anemia. The concentration of the liver extract, and further, the uniting of the stomach and liver concentrates, are definite improvements in oral liver administration. Nevertheless, these products must be taken daily and often 2 or 3 times a day. Certain patients cannot tolerate the therapy without nausea and vomiting. Others with persistent diarrhea do not effectively absorb the antipernicious anemia principle. Besides, patients in relapse obtain a more rapid reticulocyte response from parenteral liver.

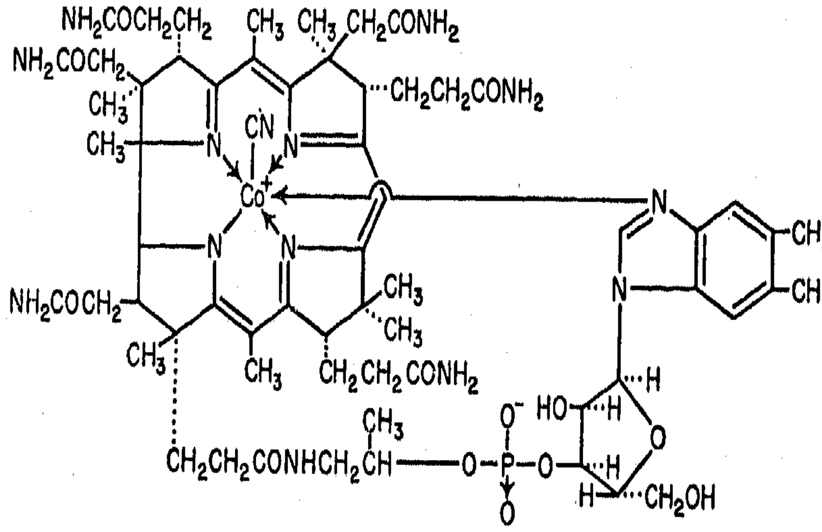
Liver extract administered parenterally need only be given once every 1 to 3 weeks for maintenance dosage. Herein lies the distinct advantage of parenteral liver. The patient is relieved of the necessity of frequent medication, and, what is more important, must return to the physician periodically for treatment and general checkup.

Although much success was achieved in the concentration of the antianemia principle of liver, efforts to isolate the principle as a chemical entity failed until 1948. Vitamin $B_{12}$ is apparently the extrinsic factor as well as the liver factor, the antipernicious anemia principle. The role of the intrinsic factor, which has been recently identified, appears to promote the absorption of vitamin $B_{12}$ from the alimentary tract.

Accordingly, in 1948 Rickes *et al.* isolated minute quantities of a red crystalline compound from liver. Shorb (1948) found that this substance, designated as vitamin $B_{12}$, assayed about 11 million L.L.D. units/mg. West (1948) showed that this substance exhibited all of the antianemia activity of liver extracts when injected into patients with pernicious anemia. One microgram appeared to be about the equivalent clinically of 1 U.S.P. injectable unit of liver extract, page 729.

The concentration of vitamin $B_{12}$ in 4 commercial injectable liver extracts was found to be not more than 0.02 per cent of the vitamin present on a dry weight basis.

**Chemical nature of vitamin $B_{12}$.** Rickes *et al.* (1948) have shown that vitamin $B_{12}$ is a red crystalline compound which contains cobalt, phosphorus, and nitrogen. It is the first substance ever isolated which is essential to life containing cobalt. The compound contains about 4 per cent of the element. The structure of vitamin $B_{12}$ is shown in the following formula:



Vitamin $B_{12}$
Cyanocobalamin, U.S.P.

**Vitamin $B_{12}$ (Cyanocobalamin, U.S.P.).** Vitamin $B_{12}$ is a cobalt-containing substance produced by the growth of suitable microbial organisms or obtained from liver. Shorb (1947) reported that two factors were essential for the growth of *Lactobacillus lactis Dorner* when the organism is maintained on a purified medium. One of these, known as the L.L.D. factor, was found in liver. Its concentration in liver paralleled the antianemia activity of the liver. The microbial test offered a new means of rapidly assaying the antianemia principle present in various liver fractions.

One gram of vitamin $B_{12}$ dissolves in about 80 ml. of water. Its maximal stability range in aqueous solution is between pH 4.5 and 5.0.

**Sources and significance of vitamin $B_{12}$.** Vitamin $B_{12}$ appears to be identical with or closely related to the "animal protein factor" (unidentified chick growth factor). Vitamin $B_{12}$ has been observed to stimulate the growth of chicks or rats when it is added to a diet which is deficient in the "animal protein factor." This growth factor is present in fish meal, cow manure, and liver. Ott *et al.* (1948) demonstrated that minute quantities of vitamin $B_{12}$ could replace

these crude sources of the protein factor in promoting chick growth.

Shorb and Briggs (1948) demonstrated the presence of vitamin $B_{12}$ by the L.L.D. test in reasonably high concentrations in digests from cow manure, fish meal, pancreatin, papain, egg white, and egg yolk. Cultures of *Streptomyces griseus* and *S. aureofaciens* have become important commercial sources of vitamin $B_{12}$.

Stokstad *et al.* (1948) obtained a positive hematologic response by administering a concentrate of the "animal protein factor" prepared from culture broths of an organism from chicken manure. Of special significance is the observation of Bethell *et al.* (1948), who found 0.3 to 1.8 $\mu$g. of vitamin $B_{12}$ activity per gram of dried feces from patients in relapse with pernicious anemia. Indeed they were able to obtain a satisfactory hematologic response in patients with pernicious anemia when extracts of these feces were injected. This study points to the basic metabolic defect in pernicious anemia, namely, *a deficiency of the intrinsic factor necessary for the absorption of vitamin $B_{12}$*.

This basic defect in pernicious anemia has been confirmed by the use of vitamin $B_{12}$ labeled with radioactive $Co^{60}$. The ingestion of 0.5 $\mu$g. of the radioactive labeled vitamin $B_{12}$ by patients with pernicious anemia results in the fecal excretion of 75 to 90 per cent of the ingested vitamin. However, when the intrinsic factor is administered simultaneously, the quantities of vitamin $B_{12}$ eliminated by fecal excretion are reduced to from 5 to 30 per cent. Vitamin $B_{12}$ containing radioactive $Co^{60}$ is official in the Pharmacopeia for use in the diagnosis of pernicious anemia based upon the foregoing phenomenon. Details of a diagnostic procedure in which the radioactive vitamin is employed are given by Schilling (1953).

**The response to vitamin $B_{12}$.** The principal value of vitamin $B_{12}$ is in the *treatment of pernicious anemia*. It appears to replace adequately liver extract in the management of the disease. Since the first report of West (1948) of the value of vitamin $B_{12}$ in pernicious anemia, numerous reports have substantiated these early observations. Patients who are sensitive to liver extracts have received the vitamin without untoward effects.

Spies and his associates (1948 *et seq.*) have demonstrated the value of vitamin $B_{12}$ in *nutritional macrocytic anemia* and *tropical* and *nontropical sprue*. It was found to be ineffective in the treatment of *puerperal macrocytic anemia*.

The use of vitamin $B_{12}$ in the promotion of growth in children has been the subject of much study and controversy (Wetzel *et al.*, 1949; Chow, 1951). The consensus appears to be that little can be achieved in growth acceleration in children who are on an adequate diet and enjoy good intestinal absorption of food, by the administration of vitamin $B_{12}$. This whole matter remains polemic. Growth is an overwhelmingly complex biologic function which appears to move at rather fixed rates in different individuals. Its terminus, maturity, is likely fixed also. One questions the advisability of metabolic alterations designed to accelerate the speed at which children grow. Will these be of aid to the child therapeutically, or benignly alter his maturity?

Vitamin $B_{12}$ has been used with some success in the *relief of pain of various neurologic origins* (Sancetta *et al.*, 1951). There is evidence that the vitamin facilitates the utilization of amino acids in the circulating blood for the formation of somatic tissues, and also assists in the production of nucleic acids in neurones. The dramatic effects of vitamin $B_{12}$ in arresting and improving the neurologic symptoms of pernicious anemia indicate that it plays an important role in neuronal metabolism. Success has been achieved with vitamin $B_{12}$ therapy in *tabetic neuralgia*, *trigeminal neuralgia*, *atypical face pain*, and *causalgic states*. For these purposes large doses of the vitamin are given intramuscularly, usually 500 to 1000 $\mu$g. daily for 2 to 3 weeks. As improvement occurs the dosage is diminished. Vitamin $B_{12}$ has been used successfully in the treatment of *diabetic neuropathy*. Urinary excretion studies have demonstrated diminished absorption of vitamin $B_{12}$ in many diabetics. It has also been noted that many diabetics are more sensitive to insulin after the administration of vitamin $B_{12}$ (Bloodworth and Hamwi, 1956). Large doses of the vitamin are employed and have been shown to be helpful in ameliorating neurologic disturbances accompanying diabetes such as *polyneuritis*, *ataxia*, *paresthesias*, and *nocturnal diarrhea*. In multiple sclerosis and amyotrophic lateral sclerosis the results of vitamin $B_{12}$ therapy have been disappointing.

**Treatment of pernicious anemia with vitamin $B_{12}$.** The use of vitamin $B_{12}$ in the treatment of pernicious anemia is a form of *replacement therapy*. *It is essential therefore that* *it be adequate*, adequate to restore the blood picture to normal, adequate to relieve the subjective symptoms, and adequate to prevent the occurrence of lesions in the spinal cord. To acquire this dosage the following facts are basic:

1. With vitamin $B_{12}$, maintenance therapy in pernicious anemia is achieved with the parenteral administration of 60 μg. every 4 weeks. A microgram of vitamin $B_{12}$ elicits the hematologic response of 1 U.S.P. unit. In cases of relapse with pernicious anemia, 15 units daily for 2 weeks, 15 units twice weekly for 3 months, then 15 units weekly for 3 months, and finally 60 to 100 units every month are given.
2. The initial treatment is almost always parenteral. After the desired hematologic response is achieved oral therapy may be instituted; however, the most satisfactory treatment is parenteral. Waife *et al.* (1963) hold the view that if parenteral therapy is not possible most cases can be controlled with massive oral doses of vitamin $B_{12}$. He recommends 300 μg. daily. Much smaller doses are effective if administered with the intrinsic factor which is lacking partially or completely in the pernicious anemia patient. Thus one can use *vitamin $B_{12}$ with Intrinsic Factor Concentrate*. This is available in tablets and capsules containing either ⅓ or ½ U.S.P. unit. One unit is recommended daily in 2 doses, ½ hour before the morning and evening meals. In cases of gastrointestinal disorders such as diarrhea, absorption may be incomplete and parenteral therapy with vitamin $B_{12}$ is indicated. Drapanas *et al.* (1963) administered vitamin $B_{12}$, $Co^{60}$-labeled with intrinsic factor to dogs and counted segments of the gastrointestinal tract for radioactivity. In physiologic doses of 1 μg. of vitamin $B_{12}$, absorption took place during 2 to 6 hours through the ileum exclusively.

There have been reports of patients with pernicious anemia who did not respond well to oral therapy with vitamin $B_{12}$ and the intrinsic factor. The refractoriness may develop upon prolonged administration of the preparation The most certain form of therapy is the intramuscular injection of vitamin $B_{12}$; in addition, it has the advantage of bringing the patient to the physician for observation at fixed time periods. Parenteral injections of vitamin $B_{12}$ in large quantities are excreted rapidly in the urine and are not fully available for utilization by the hematopoietic system. It is of interest, however, that the diagnostic Schilling test, which requires an injection of large amounts of vitamin $B_{12}$, often results in marked temporary relief of the hematologic symptoms. It has been shown that a tannate derivative of vitamin $B_{12}$, "Depinor," was more slowly absorbed from the depot of injection, and therefore, significantly greater and more sustained blood levels of the vitamin were achieved.

In former years large quantities of liver extracts, 12 to 25 gm. daily, were required to achieve those therapeutic ends which are comparatively easy to accomplish with microgram quantities of vitamin $B_{12}$.

In the presence of neurologic symptoms the dosage of vitamin $B_{12}$ should be increased. Intensive therapy of 100 to 500 μg. daily is indicated for about 2 weeks. Thereafter improvement should be maintained by biweekly injections of 500 to 1000 μg. of the vitamin.

Large doses of vitamin $B_{12}$ have not manifested toxic symptoms. There appears to be no danger of producing polycythemia. Although a fatal case of polycythemia following pernicious anemia treated with vitamin $B_{12}$ was reported, the opinion was expressed that the coexistence of the two diseases in the same individual was coincidental.

By using radioactive cobalt in the vitamin it was determined that a single intramuscular dose is rapidly excreted by the kidneys and to a lesser degree by the gastrointestinal tract (Rosenblum *et al.*, 1952). Within 8 hours a significant portion of the vitamin is excreted. Divided daily doses provide a longer sojourn of the vitamin in the body.

**Vitamin $B_{12}$ versus liver extract in pernicious anemia.** For what it was, rather than for what it is, the foregoing discussion of liver extract therapy in pernicious anemia was considered. Vitamin $B_{12}$ has almost completely replaced liver extract in pernicious anemia. Vitamin $B_{12}$ will not do more than an equivalent amount of liver extract. However, the vitamin is a more uniformly standardized agent. It is not irritating to tissues when injected. It rarely produces allergic responses as might occur in therapy with liver. Unless future work uncovers some factor of benefit to the patient with pernicious anemia present in liver other than vitamin $B_{12}$, vitamin $B_{12}$ is the therapy of choice.

The standardization of vitamin $B_{12}$ is directed by the U.S.P. to be carried out on microorganisms. One microgram of the vitamin is a U.S.P. unit. Liver preparations are standardized on patients with pernicious anemia. One U.S.P. unit is the *minimal amount which when given daily to a suitable patient with pernicious anemia in relapse will cause an adequate hematopoietic response.*

**Effects of vitamin $B_{12}$ therapy.** Vitamin $B_{12}$ preparations effect a remission in the symptoms of pernicious anemia. The blood picture returns to normal and can be so maintained by adequate dosage. The megaloblastic hyperplasia ceases. Pathologic megaloblasts, characteristic of the disease, are removed from the bone marrow. They are replaced by cells of the normoblastic series.

Neurologic symptoms, if present, do not progress and may be greatly diminished by the administration of vitamin $B_{12}$.

The nausea, vomiting, and diarrhea are also relieved by vitamin $B_{12}$ therapy. The glossitis is ameliorated, but the achlorhydria does not disappear upon therapy. Therefore it may be necessary to administer diluted hydrochloric acid or a preparation providing free hydrochloric acid, such as Acidulin, for peptic digestion.

**Hydroxocobalamin, AlphaRedisol.** Many efforts have been made to prolong the high blood levels of vitamin $B_{12}$ following the intramuscular injection. This can be achieved by a depot injection in water or oil with aluminum monostearate or with a zinc tannate complex. The principal advance in this area has been the modification of the vitamin $B_{12}$ molecule producing hydroxocobalamin. This compound is cyanocobalamin in which the cyano group has been replaced by a hydroxyl group. Its effectiveness is equivalent to the parent compound. Hydroxocobalamin is quite alkaline in solution (pH 12); however, upon standing a molecular rearrangement occurs, producing an acid solution (pH 2). The formulation AlphaRedisol contains hydroxocobalamin neutralized and stabilized with acetate buffers.

A disadvantage of parenteral vitamin $B_{12}$ therapy stems from the fact that depleted body stores are not readily restored. With large parenteral doses most of the vitamin is excreted in the urine within the first 12 hours. This does not prevail with hydroxocobalamin; it appears to be more readily stored and less slowly excreted. For example, after the intramuscular injection of the 2 agents containing $Co^{60}$ at levels of 500 to 1000 μg., the retention of hydroxocobalamin was 3-fold that of vitamin $B_{12}$ during the first 72 hours. No significant urinary or stool excretion occurred with hydroxocobalamin after 72 hours (Killander and Schilling, 1960).

The longer retention of hydroxocobalamin by the tissues and the maintenance of high blood levels for longer periods has been confirmed by numerous investigators. Glass *et al.* (1963) injected 50 persons with vitamin $B_{12}$ and Alpha-Redisol and compared the blood levels during 10 to 14 weekly injections. With vitamin $B_{12}$ the blood levels remained in the range of 1000 to 1700 μμg./ml.; with hydroxocobalamin, they leveled at an average of 8000 μμg./ml. Of special significance is the slow return to normal levels with hydroxocobalamin (6 to 7 months), contrasted with 4 to 5 weeks with vitamin $B_{12}$. It is clear that with this modification of vitamin $B_{12}$ the tissues can be saturated with 8 to 10 injections of 1000 μg. of medication in pernicious anemia. This possibility must be more thoroughly explored before it can be established as a definitive regimen of treatment. In our opinion hydroxocobalamin represents a signal advance in the treatment of pernicious anemia.

**Vitamin $B_{12}$ and the Castle hypothesis.** Numerous investigators have observed that the oral administration of vitamin $B_{12}$ was without marked effect on the hematologic picture of pernicious anemia. When, however, the vitamin was administered orally with human gastric juice it was effective. The Castle hypothesis, page 725, considered that tissue such as beef muscle contained the extrinsic factor of the antipernicious anemia principle which produces little or no hematologic response when administered to a patient with pernicious anemia. When normal gastric juice was administered with it (intrinsic factor), the antianemia principle was formed.

The interpretation of the Castle hypothesis in light of the discovery of vitamin $B_{12}$ is most interesting. As has been stated, vitamin $B_{12}$ is active parenterally in a dose of 1 μg. Orally, many times this dose is ineffective. These dosage levels were effective, however, when the vitamin was administered with normal gastric juice. Rickes *et al.* (1948 *et seq.*) attempted to follow the action of human gastric juice on vitamin $B_{12}$. They assayed normal human gastric juice for the L.L.D. activity of vitamin $B_{12}$. It assayed 100 units/ml. Large volumes of gastric juice (equivalent to 3 μg. of vitamin $B_{12}$) produced no hematologic effect in pernicious anemia patients. It was shown that gastric juice concentrates, however, when administered parenterally, were active against pernicious anemia, thus establishing the vitamin $B_{12}$ activity of gastric juice.

The intrinsic factor has not been isolated in a pure form. Much has been done recently to shed light upon its role in the hematopoietic system and its relationship to vitamin $B_{12}$. Fox and Castle (1942) showed that in man the factor is secreted mainly by the fundic portion of the stomach. In pernicious anemia this factor is not necessarily completely absent. Indeed it has been shown that the pooled small volume secretions of the stomachs of the patients with pernicious anemia in relapse, when administered with beef muscle, were able to produce a favorable hematologic response in other pernicious anemia patients. Thus it is clear that the response in pernicious anemia to oral vitamin $B_{12}$ therapy will vary greatly from patient to patient. It is estimated that the oral effective dose to vitamin $B_{12}$ in pernicious anemia administered *without gastric juice concentrate* (*intrinsic factor*) is *30* to *60* times more than the parenteral dose.

The effect of gastric juice on vitamin $B_{12}$ was studied by various procedures. After the incubation of the vitamin in gastric juice at pH 2 there was no change in absorption spectrum or microbiologic activity (L.L.D. activity). Indeed the vitamin was recovered in a crystalline form from the mixture. Wolf *et al.* (1950) concluded that there was no evidence for a chemical reaction between vitamin $B_{12}$ and the intrinsic factor which resulted in a gross chemical change in vitamin $B_{12}$. Lajtha (1950) is of the opinion that the intrinsic factor is involved in the activity of vitamin $B_{12}$ on the bone marrow, in addition to promoting its absorption through the gastrointestinal tract. Megaloblasts will not mature *in vitro* in the presence of vitamin $B_{12}$ unless a small amount of gastric juice is present. Heathcote and Mooney (1958) state, "Since crystalline vitamin $B_{12}$ alone cannot bring about maturation, vitamin $B_{12}$ seems to be more acceptable nutritionally for maturation when combined as a peptide complex and is, in this form, a closer approximation to the anti-pernicious-anemia factor of liver than is the purified vitamin."

Latner (1954) isolated a gastric mucoprotein which is likely to be the intrinsic factor. The substance has a molecular weight of the order of 15,000. The compound binds vitamin $B_{12}$, and promotes its gastrointestinal absorption in patients with pernicious anemia. Thus it appears that the Castle hypothesis has been substantiated, first by the isolation of vitamin $B_{12}$, and second by the separation of the gastric mucoprotein, the *intrinsic factor.*

The absorption of vitamin $B_{12}$ has been divided into three phases (Cooper and Castle, 1960). First, as previously discussed, is the binding of vitamin $B_{12}$ to the intrinsic factor. The affinity of the intrinsic factor for the vitamin is such that binding takes place even if the vitamin is already complexed with other proteins. Second is the attachment of the vitamin $B_{12}$-intrinsic factor complex to the ileum mucosa. This process is enhanced by the presence of calcium ions.

Transport of vitamin $B_{12}$ across the intestine into the blood is the third phase of absorption. The release of the vitamin from the intrinsic factor complex is apparently a species-specific enzymic process. A delay of several hours occurs while the vitamin remains in the intestinal wall before entering the blood. The fate of the vitamin during this phase has not yet been fully elucidated.

**Vitamin $B_{12}$ and Folic acid.** Evidence points to most conditions of anemia as resulting from some nutritional deficiency. The inter-relationships which have been shown to exist between vitamin $B_{12}$ and folic acid in the hematopoietic system emphasize this view. When vitamin $B_{12}$ is injected in patients with pernicious anemia, this vitamin plus folic acid released from the liver causes a reversal of the megaloblastic arrest of the bone marrow. The necessity for the intervention of folic acid can be established by administering a folic acid antagonist along with vitamin $B_{12}$. No hematologic response is elicited. The action of folic acid in the bone marrow has been blocked. Indeed, swine fed a diet deficient in folic acid plus vitamin $B_{12}$ soon developed a severe macrocytic anemia, indicating the typical megaloblastic arrest of the bone marrow. Indeed vitamin $B_{12}$ and folic acid act at different stages of the synthesis of nucleoproteins, and a deficiency of either or both manifests itself in many cellular abnormalities. The one which is readily recognized is the megaloblastic bone marrow. Folic acid seems to be particularly involved in desoxyribonucleic acid (DNA) synthesis, whereas vitamin $B_{12}$ is necessary for DNA and ribonucleic acid (RNA) production. Thus folic acid will supply the DNA required to the bone marrow, but vitamin $B_{12}$ is essential for RNA synthesis required for the arresting of the neurologic symptoms of pernicious anemia.

Thus it appears that both vitamin $B_{12}$ and folic acid are necessary for erythropoiesis. Vitamin $B_{12}$ renders the endogenous folic acid available for the bone marrow. The active available form of folic acid appears to be *leucovorin*, and the first step in the process of converting folic acid into this active form is one of reduction. Folic acid is reduced to tetrahydrofolic acid by the intervention of reduced diphosphopyridine nucleotide. It then acts as an acceptor of a one-carbon unit combining with a molecule of formate and becoming the 5-formyl derivative of 5,6,7,8-tetrahydrofolic acid which is the *citrovorum factor*, *leucovorin* or folinic acid. This is the biologically active form of folic acid. It appears that ascorbic acid also plays a role in this reduction of folic acid and that vitamin $B_{12}$ also facilitates the transformation.

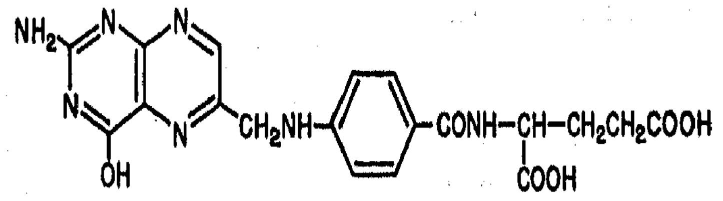
Vitamin $B_{12}$ and folic acid have been shown to exhibit a common biochemical transformation, *i.e.*, the utilization of single carbon fragments. This has been shown by feeding rats on special diets (free of labile methyl groups) and sulfasuxidine. Homocystine served as the precursor of methionine. Both vitamin $B_{12}$ and folic acid were necessary in the diet for the maintenance of growth. Methionine was an adequate substitute for vitamin $B_{12}$ and folic acid. It is therefore suggested that vitamin $B_{12}$ and folic acid supplement each other in the methylation of homocystine, possibly at the expense of serine and glycine (Bennett, 1950). More recent studies indicate that methionine synthesis requires 5-methyltetrahydrofolate, a vitamin $B_{12}$-protein complex and ATP, $Mg^{++}$, FAD, and DNPH as cofactors.

It is clear that vitamin $B_{12}$ plays a multiplicity of roles in the metabolic pathways of nucleic acid synthesis. Besides, there is evidence that it influences the metabolism of carbohydrates, amino acids, and fats. Some of these actions of vitamin $B_{12}$ are dependent upon its effect upon sulfhydryl-containing compounds such as glutathione and coenzyme A. It is possible that insufficient vitamin $B_{12}$ levels in the tissues would result in the failure of coenzyme A to be reduced from its S-S to its SH form, and thus affect the utilization of labile methyl groups. Other liver enzymes which are dependent upon vitamin $B_{12}$ for their activity are xanthine oxidase and a transmethylase.

### Folic Acid

Various investigators succeeded in isolating from different natural sources a potent nutritional factor. This substance, obtained from liver, yeast, and spinach, was found to be essential for the growth of *Lactobacillus casei*, for hemoglobin formation and growth of chicks, and for the prevention and cure of nutritional cytopenia in monkeys. This factor has been called *vitamin M*, *vitamin Bc*, *eluate factor*, *Lactobacillus casei factor*, and *folic acid.*

A substance identical with the *Lactobacillus casei factor* was synthesized by Angier *et al.* (1946). It was called folic acid. The term *pteroylglutamic acid* has been chosen as a suitable chemical name for folic acid. The structure of the compound is shown in the accompanying formula.

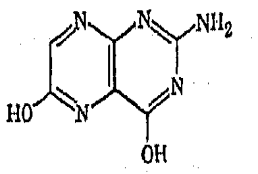


Folic Acid, U.S.P.

It may be observed that the molecule contains 3 distinct groupings: (a) glutamic acid, (b) *p*-aminobenzoic acid, and (c) a pteridyl ring. The folic acid in foods is composed of conjugates of this structure with additional molecules of glutamic acid and hence of higher molecular weight. The vitamin conjugate was isolated by Pfiffner *et al.* (1945). The conjugate has 7 molecules of glutamic acid in the molecule and has a molecular weight of 2.8 times that of folic acid. Heinle and Welch (1946) and others showed that individuals having macrocytic anemia are incapable of degrading these conjugates into folic acid. Indeed folic acid deficiency can be induced in rats by adding 1 per cent of succinyl sulfathiazole to the food. This probably acts by inhibiting the normal production of folic acid by intestinal organisms. It therefore appears possible that the antianemia principle of the liver in normal persons may be responsible for the conversion of these conjugates into folic acid.

Folic acid appears to be an essential nutrient for the functioning of the bone marrow. Folic acid deprivation in the diets of chicks and monkeys has been shown to produce characteristic anemias. In man, folic acid deprivation leads to macrocytic anemia. As has been stated previously, the role played by folic acid as an essential nutrient to the bone marrow apparently occurs after the conversion of folic acid to leucovorin or folinic acid. In this conversion reduced diphosphopyridine nucleotide, vitamin $B_{12}$, and ascorbic acid play an important function (page 730). Folinic acid is 5-formyl-5,6,7,8-tetrahydropteroyl-glutamic acid. In cases of macrocytic anemia refractory to folic acid, it may be valuable. For example, in the macrocytic anemia accompanying scurvy, Castle (1951) found folinic acid effective, but folic acid was effective only when administered with adequate ascorbic acid therapy. Folinic acid is also quite effective in combating the effects of folic acid antagonists.

**Biosynthesis of folic acid.** Since the conjugate of folic acid present in certain foods is not available to persons with macrocytic anemia, the question arose as to whether or not they could use the fragments of the folic acid molecule to synthesize the compound. Accordingly Spies (1947) gave individuals with macrocytic anemia daily oral doses of 5 gm. each of *p*-aminobenzoic acid and glutamic acid; in addition, 500 mg. of xanthopterin was given daily. Xanthopterin has the following chemical constitution and closely resembles the pteroyl portion of the folic acid molecule.



Xanthopterin

These molecular fragments were incapable of eliciting the hematopoietic response in persons with macrocytic anemia. On the other hand, 10 mg. daily of folic acid caused a dramatic response in the same individuals.

Following the same type of reasoning, Spies injected 5 mg. of pteroic acid intravenously into a patient with pernicious anemia. No hematopoietic response was elicited. Pteroic acid is the molecule of folic acid minus the glutamic acid molecule. The same patient responded spectacularly to 5 mg. of folic acid. It appears, therefore, that patients with macrocytic anemia require the intact molecule of folic acid for the proper functioning of their hematopoietic systems. This they are incapable of synthesizing from its molecular fragments.

**Folic acid and vitamin $B_{12}$ in pernicious anemia.** Folic acid and vitamin $B_{12}$ separately and spectacularly stimulate the hematopoietic system, causing a return to normal of the blood picture. *Vitamin $B_{12}$ checks and often mitigates the neurologic symptoms. Under folic acid therapy these symptoms progress.* It is evident, therefore, that folic acid may be considered possibly as only an adjunct to vitamin $B_{12}$ in the treatment of pernicious anemia and never a substitute for it.

The metabolic activities of folic acid and vitamin $B_{12}$ do not appear to be limited to hemopoieses. They are likely involved in the synthesis of all body proteins. Perhaps their deficiency is manifested first in red cell formation, owing to the enormous amount of protein synthesis involved in red cell production.

**Folic Acid, U.S.P.** Folic acid occurs as a yellow or yellowish orange, odorless crystalline powder. The acid is insoluble in water. It is administered in tablets and capsules of 10 mg. as a daily dose.

**Therapeutic uses of folic acid.**

1. The principal use of folic acid is in the treatment of *nutritional macrocytic anemia.* It promptly restores the hematologic picture to normal and effects amelioration of the symptons of the deficiency. The effective dose is 5 to 20 mg. daily by mouth. It may be administered intramuscularly, but the parenteral use of folic acid offers no advantage in most cases.
2. Folic acid is useful in the treatment of *sprue.*
3. Folic acid has been found useful also in the *macrocytic anemias of pregnancy and pellagra.*

**Calcium Leucovorin, U.S.P.** Calcium leucovorin occurs as a yellowish white or yellow, odorless, microcrystalline powder. It is soluble in water. This derivative of folic acid was discussed previously on page 730 as the active form, into which folic acid is converted prior to exerting its effect upon the bone marrow. It is the *calcium salt of 5-formyl-5,6,7,8-tetrahydrofolic acid* and is known as *calcium folinate* and the *citrovorum factor.* Its principal use is in the amelioration of the toxic symptoms of folic acid antagonists used in the treatment of leukemia, page 735. It is administered intramuscularly in a dose of 3 to 6 mg. daily as long as the toxic symptoms persist. The drug may also be used intramuscularly in the treatment of megaloblastic anemias similarly to folic acid. For this purpose the daily dose is 10 mg.

### POLYCYTHEMIA

It is well known that an increase in the number of red cells in the blood will occur as a compensatory measure. The classic example of this is the response of the bone marrow to a lowered oxygen tension of the blood such as occurs upon ascending high altitudes.

This condition may occur, however, as a primary pathologic state and not a physiologic normal response to compensate for other influences. This disease is called *polycythemia vera.* There are other synonyms for it such as *erythemia* and *Vaquez-Osler disease.* The primary involvement is the bone marrow. It is increased in quantity and is hyperplastic. The number of red cells in the peripheral blood may increase to 8 or even 14 million/cu. mm. The red cells show no special irregularity in shape, and the number of reticulocytes is not greatly increased. The sedimentation rate is generally zero.

Some of the precipitating factors in polycythemia vera are residence at high altitude, congenital cyanotic heart disease, pulmonary arteriovenous fistula, chronic pulmonary disease, methemoglobinemia, and the ingestion of cobalt salts.

The symptoms from this greatly increased hemoconcentration are *weakness, lassitude, vertigo,* and *cyanosis.* The great viscosity of the blood predisposes the individual to circulatory collapse.

**Treatment of polycythemia.** Polycythemia vera is a disease of unknown etiology. Therefore at present a chemotherapeutic attack on the basic biochemical lesion is impossible. Since most of the symptoms are produced by the increase in blood volume and mass of red cells, the most physiologic treatment at present is the reduction of these factors. In some cases of the disease the symptoms are mitigated by *systematic venesection.* In refractory cases and cases where thrombosis occurs, drug therapy is indicated. There are certain compounds which are industrial hazards owing to their deleterious effect upon the bone marrow. These substances, such as *benzene* and *phenylhydrazine,* have been employed successfully as drugs in the treatment of the disease. These have been abandoned in favor of radioactive phosphorus.

**The nature of radioactive phosphorus.** When a neutron is shot into the nucleus of the atom of a stable element the nucleus may be so altered that it becomes radioactive. To illustrate, the nucleus of a stable phosphorus atom contains 15 protons and 16 neutrons. This gives the atom a total mass of 31 or $P^{31}$. By bombardment of the nucleus of $P^{31}$ with a high-speed charged particle like deuteron, the proton with a positive charge will be repelled, but the neutron without a charge may enter the nucleus of the $P^{31}$ atom. The atom of phosphorus now has 17 neutrons and is $P^{32}$. The nucleus is now unstable, *i.e.,* radioactive.

The atoms of the radioactive element $P^{32}$ undergo a nuclear transformation with the emission of an electron. They then become stable sulfur atoms. It is the electron discharge of the $P^{32}$, beta ray emission, which affects tissues. The effect has proved to be valuable in the treatment of certain diseases of which polycythemia is typical.

The radioactive phosphorus is generally employed in the form of $Na_2HPO_4$ in which P is $P^{32}$. It is injected intravenously in the form of an isotonic solution or given orally. The salt is common to the blood and tissue cells when P is $P^{31}$. Therefore the salt with the radioactive atom is readily transported to all parts of the body. The rate of uptake of the radioactive substance is dependent upon 3 factors:

1. The total exchangeable phosphorus content of the tissues;
2. The rate of turnover of exchangeable phosphorus in the tissue;
3. The rate at which new tissue is laid down.

Accordingly, bone will be markedly affected by the $P^{32}$ because it is rich in phosphorus. Liver and brain enjoy a rapid turnover of phosphorus. The turnover in the liver is more rapid than that in the brain, and the former takes up much of $P^{32}$. Neoplastic tissue is rapidly laid down and invariably takes up more of $P^{32}$ than normal tissue of the same type.

The maximal range of penetration of the beta rays from $P^{32}$ is 0.7 cm. Most electrons travel a much shorter distance. Therefore, the electron bombardment will be confined for the most part to the tissues surrounding the concentration of the radioactive phosphorus.

The half-life period of $P^{32}$ is 14.3 days. This is of great convenience in therapy, for after 2 weeks most of the $P^{32}$ has decayed or been excreted and the electron emission has nearly ceased.

**Radioactive phosphorus in polycythemia.** The standardized method of treatment with $P^{32}$ is carried out as follows (Wiseman, 1954):

> The initial dose of radioactive phosphorus is 4.5 millicuries (mc.) if the red cell count is over 9 million, 4 mc. with counts of 8 to 9 million, 3.5 mc. with counts of 7 to 8 million, and 3 mc. with counts of less than 7 million. This is the oral dose and it is most effective if the stomach is devoid of food. The intravenous dosage schedule is 25 per cent less and each dosage may be reduced by 1 mc. if the platelet count is not elevated.
>
> The blood should be checked monthly for red cells, white cells, and platelets.
>
> A second dose should not be given at an interval of less than 2 months.

Circulating blood cells are not directly affected by $P^{32}$; therefore, about 3 months are required for the maximal reduction of the red cell count. In most patients 2 doses of $P^{32}$ maintain red cell levels of 5 to 6 million for about 2 years before another treatment is necessary.

Radioactive phosphorus is official in the Pharmacopeia as *Sodium Radiophosphate* (*$P^{32}$*) *Injection*. It is usually available as follows: 0.5 to 7.0 mc. as ordered for the individual needs of the patient, in a volume suitable for the need of the patient.

Reports from various clinics on the use of $P^{32}$ in polycythemia have been uniformly good. The criticism of the use of $P^{32}$ in polycythemia has been that later these patients may develop leukemia. Masouredis and Lawrence (1957) studied the problem of leukemia occurring in patients with polycythemia. Of 179 patients with polycythemia, 22 had developed a "leukemic" type of picture either terminally or during the follow-up period. Their findings show that the tendency to develop leukemia is evident before $P^{32}$ therapy. It appears that the leukemic predisposition is present in a segment of polycythemic patients prior to $P^{32}$ therapy. Their data are inadequate to exclude completely the relationship between $P^{32}$ therapy in polycythemia and leukemia. Nevertheless, the increased life span, decrease in deaths owing to hemorrhage or thrombosis, simplicity of medication, and minimal side effects establish $P^{32}$ as the drug of choice in polycythemia.

Other drugs having limited use in the treatment of polycythemia are pyrimethamine and busulfan; for a discussion of their use see page 1131, 5th edition.

### LEUKEMIA

Leukemia is a hyperplasia of the leukocyte-producing tissues, usually with marked and persistent changes in the leukocytes of the circulating blood. There is a tenderness of the sternum and shins. Enlargement of the spleen and lymph nodes occurs. The disease is accompanied by progressive anemia, internal hemorrhage, and complete exhaustion. There are numerous varieties of the disease recognized. The most prevalent types are *chronic myelocytic leukemia*, *chronic lymphocytic leukemia*, and *acute leukemia*.

Acute leukemia occurs in all age groups; however, about half the cases are in persons who are over 15 years. The incidence of all types of leukemia is increasing in the United States; it is estimated that 11,000 new cases of leukemia are encountered each year in this country (Ellison and Burchenal, 1957).

Older therapy consisted of the use of Fowler's solution of arsenic. Modern therapy in leukemia consists of a choice of many different agents. The treatment of leukemia with various types of chemotherapeutic agents may be divided into the following categories:

1. Antimetabolites—Aminopterin, mercaptopurine, etc.;
2. Ionizing radiations—X-ray and $P^{32}$;
3. Polyfunctional alkylating agents, (cytotoxic agents)—Triethylenemelamine, busulfan, etc.;
4. Steroid hormones—ACTH, cortisone, etc.;
5. Antibiotics—Azaserine.

Although this group of therapeutic agents has been responsible for prolonging the life of patients with leukemia, at best their action is palliative. None of the agents, separately or combined, cures the disease.

In acute leukemia the antimetabolites with ACTH and corticosteriod hormones achieve the most certain and longest remissions. In chronic lymphocytic leukemia, ionizing radiation (x-ray and radioactive phosphorus) and the polyfunctional alkylating agents appear to be most effective. In the treatment of chronic myelogenous leukemia likewise, ionizing radiation and the polyfunctional alkylating agents have achieved the best results. Adjunctive treatment includes folic acid antagonists, especially in children, and corticosteroids.

### FOLIC ACID ANTAGONISTS

Folic acid has been shown by many investigators to be an essential growth factor for a number of bacterial species. It appears to be important in nucleoprotein metabolism. Animal nutritional studies have demonstrated that a folic acid deficiency will lead to *anemia*, *granulocytopenia*, *diarrhea*, and *death*. At autopsy these animals exhibit a marked hyperplasia of the bone marrow. These changes are reversible in folic acid deficiency states by the administration of adequate dosage of folic acid. It has been observed that animal and human neoplasms contained a higher level of folic acid than did normal tissue. Various workers reported the activity of folic acid in retarding growth and causing regression of mouse sarcomas. Therefore the possibility of producing compounds related structurally to folic acid for trial in neoplastic disease suggested itself.

**Aminopterin.** A vast number of folic acid derivatives have been synthesized. Many substances closely related to folic acid have been shown to antagonize the biologic activity of the acid. Among these substances is *aminopterin*. Little *et al.* (1948) were able to produce an inhibition of the growth of Rous sarcoma in chicks by the feeding of aminopterin. Others have confirmed the fact that this folic acid antagonist caused an inhibition of growth in various animal neoplasms. For example, Burchenal *et al.* (1949) tested 90 compounds related to folic acid for their chemotherapeutic effect against transmitted leukemia in mice. Only 4 showed a slight to moderate effect.

The observation of the neoplastic growth-inhibiting effect of aminopterin, and the studies by Farber *et al.* (1948) indicating that leukemia was aggravated by the administration of folic acid, prompted the use of aminopterin in *leukemia*.

Condit (1961) showed that in the mouse liver *in vivo* the conversion of exogenous folic acid to compounds with citrovorum factor activity is inhibited completely by levels of aminopterin of the same order of magnitude as those bound to the enzyme folic acid reductase *in vitro*. Owing to the fact that this quantity of folic acid is several thousand times smaller than the $LD_{50}$, he concluded that toxic effects evoked by larger doses stem from another mechanism of action.

Aminopterin is 4-aminofolic acid, page 731. It occurs in clusters of yellow needles. It is soluble in water in the presence of sodium hydroxide.

**Aminopterin in leukemia.** There are several critical accounts of the use of aminopterin in leukemia. In general, it appears that in chronic leukemia neither aminopterin nor any other folic acid antagonist has given encouraging results. There seems, however, to be a consensus that in acute leukemia the use of aminopterin in some cases may produce a temporary remission of the clinical and hematologic symptoms. For example, Farber (1951) observed a remission rate of 68 per cent in 190 patients with acute leukemia when aminopterin was used. This far exceeds the spontaneous remission rate. Burchenal (1952) observed that those cases of acute leukemia treated in the Memorial Hospital, New York, 1926–47, experienced a mean survival time of 4 to 5 months. With folic acid antagonist therapy the survival time since 1947 increased to 16.9 months. During the periods of remission the evidence of the disease process is nearly always absent, and the patients usually carry on their daily activities. Remission rates in children are much higher than those in adults. In the latter category the remission rate is about 5 per cent.

Folic acid antagonists as a rule elicit severe untoward symptoms. The utmost care must be exercised in their administration. *Ulcerative stomatitis* usually heralds overdosage. Other symptoms are *anorexia*, *abdominal pain*, and *diarrhea*. These symptoms may be ameliorated by 10- to 30-mg. doses intramuscularly of leucovorin (Barnard and Freeman, 1954). *Bone marrow depression* with *leukopenia*, *thrombocytopenia*, and *bleeding* are serious complications of therapy with folic acid antagonists.

The dosage schedule for aminopterin recommended is 0.5 to 2 mg. daily intramuscularly until remission occurs. Oral doses of 0.5 mg. are frequently employed also.

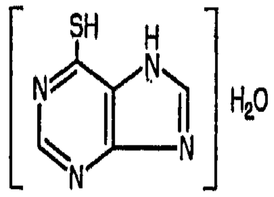
**Methotrexate U.S.P.** This compound, which was formerly called α-Methopterin, is another folic acid antagonist which elicits a response similar to aminopterin. Chemically, methotrexate is 4-amino-10-methyl-folic acid. It appears to be less toxic than aminopterin. It is used in the acute leukemia of childhood in doses of 2.5 to 5 mg.

daily. In a period of 2 to 8 weeks hematologic improvement has been noted in 50 per cent of the cases. In adults the agent is far less effective. The side effects with methotrexate are similar to those with aminopterin; however, they appear to be less severe.

Methotrexate occurs as an orange-brown, odorless, crystalline powder which is insoluble in water.

As previously stated, page 735, it appears that folic acid antagonists block the conversion of folic acid to folinic acid. ACTH and cortisone will also afford temporary remission in leukemia. Their response is not so marked or dependable as that of the folic acid antagonists. The administration of ACTH or the corticosteroids in conjunction with folic acid antagonist therapy appears to be established as a means of increasing the effectiveness of these antimetabolites in the treatment of leukemia.

**Mercaptopurine, U.S.P.** Mercaptopurine or purinethol is an analog of the nucleic acid constituent adenine and the physiologic purine base hypoxanthine. Its structure is shown in the accompanying formula.



Mercaptopurine, U.S.P.
6-Purinethol

Mercaptopurine occurs as a yellow, crystalline powder, which is insoluble in water.

The compound was synthesized by Hitchings *et al.* (1950) and studied clinically by Burchenal and his associates (1954) in the treatment of acute leukemia and chronic myelogenous leukemia. The drug has not been found to be of value in chronic lymphatic leukemia, and it is not indicated in the treatment of solid tumors.

Hitchings and his associates (1950) prepared this and other compounds for their possible chemotherapeutic activity based upon the probability that interference with nucleic acid synthesis would probably be more damaging to parasitic than to normal tissues.

Mercaptopurine has been shown in microbiologic studies to be an antagonist to both hypoxanthine and adenine. The fact that mercaptopurine has been active clinically in certain antifolic-resistant leukemias appears to indicate that its mechanism of action is based upon its antipurine rather than an antifolic acid action.

**Mercaptopurine in leukemias.** Mercaptopurine, like other agents used in leukemias, will vary from patient to patient as far as optimal dosage and absence of side effects are concerned. The usual initial dose is about 2.5 mg./kg. orally, which is approximately 100 to 200 mg. in the average adult and 50 mg. in the average 5-year-old child. The drug is continued daily for several weeks or more in some patients. If after 4 weeks of this dosage there is no clinical improvement and no evidence of leukocyte depression, the dosage may be increased to 5 mg./kg. daily.

In 1954 a conference on the status of mercaptopurine was held at the New York Academy of Science. In summary, it appears that mercaptopurine is without beneficial effect in metastatic carcinomas, sarcomas, Hodgkin's disease, lymphosarcoma, and chronic lymphocytic leukemia. In the early stage of chronic myelocytic leukemia the drug produces a high percentage of remissions. When mercaptopurine is used in sequence with other agents it is capable of prolonging life in children with acute leukemia.

The principal toxic effect of mercaptopurine is to the hematopoietic system, producing *leukopenia* and, with excessive doses, *thrombocytopenia* and bleeding. The dosage must be cautiously controlled since the effect on the blood count may be delayed several days. Therefore, one is warned to discontinue mercaptopurine temporarily at the first evidence of a fall in the white cell count.

There appears to be no known antagonist to mercaptopurine, and when toxicity to the drug develops, medication should be immediately withdrawn. Like the folic acid antagonists, mercaptopurine may provide a temporary remission, either partial or complete, in acute leukemia and chronic myelogenous leukemia. Granville *et al.* (1958), from their studies of a series of 20 adult patients with acute leukemia, consider mercaptopurine the promising therapeutic agent. Combining the mercaptopurine treatment with large doses of prednisone gave the most satisfactory results.

**6-Chloropurine.** 6-Chloropurine is a newer antimetabolite useful in the treatment of acute and chronic myelocytic leukemia. Burchenal *et al.* (1953) studied the drug in man and found it useful in the treatment of leukemia. Ellison *et al.* (1958) studied 6-chloropurine in patients with leukemia who did not respond to mercaptopurine. These patients did not respond to 6-chloropurine. From their studies in other cases, they concluded that 6-chloropurine was slightly superior to mercaptopurine in acute leukemia in adults. The pattern of response indicated that the 2 antimetabolites have a similar mechanism of action and range of therapeutic activity. 6-Chloropurine is usually administered in daily doses of 11 to 20 mg./kg. The largest daily dose was 38 mg./kg.

Another antimetabolite which appears to have limited use in leukemia is 6-thioguanine. Its oral dose is 2.5 mg./kg. daily.

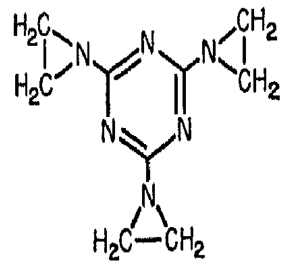
### Ionizing Radiations and Radioactive Phosphorus

The biologic effects of ionizing radiations are discussed in chapter 57. X-rays and radioactive phosphorus are of definitive value in the treatment of chronic myelocytic and monocytic leukemia. Reinhard *et al.* (1959) reviewed their results in 102 patients with chronic lymphocytic and chronic granulocytic leukemia treated with $P^{32}$ over a 15-year period. The 5-year survival period was 51 per cent for lymphocytic leukemia and only 12.5 per cent for granulocytic leukemia.

### Polyfunctioning Alkylating Cytotoxic Agents

Cytotoxic agents have been used in the treatment of leukemia since Lissauer first used arsenic compounds in the disease in 1865. Indeed, Fowler's solution of potassium arsenite is used today in many areas in the treatment of leukemia. However, it has been replaced by the more effective *polyfunctioning alkylating agents*, which, like arsenic, are cytotoxic. The first one of these agents to be generally used in leukemia and other neoplastic diseases was *nitrogen mustard* or *mechlorethamine hydrochloride*. Since the principal use of this compound at present is in the treatment of solid tumors, its action and use are discussed on page 911. Attempts to reduce the systemic toxicity and increase the effectiveness of mechlorethamine have resulted in the synthesis and use in leukemia of Triethylenemelamine, Chlorambucil and other cytotoxic agents.

**Triethylenemelamine U.S.P. (TEM).** This substance was synthesized in an attempt to prepare a more satisfactory agent than nitrogen mustard in the treatment of neoplastic diseases. Its structure is shown in the accompanying formula.



Triethylenemelamine, U.S.P. (TEM)
[2,4,6-Tris(1-aziridinyl)-*s*-triazine; 2,4,6-Tris-(ethylenimino)-*s*-triazine]

Triethylenemelamine occurs as a white, crystalline powder which is freely soluble in water.

TEM is related to nitrogen mustard when it is transformed into the ethylene-imine rings which are considered the active cytotoxic groups. It is recommended in the treatment of *lymphomas*, *chronic myelogenous leukemia*, *chronic lymphatic leukemia*, *Hodgkin's disease*, *malignant lymphoma*, and *certain other malignancies*. It is active orally as well as parenterally. *Nausea* and *anorexia* are common untoward side effects. Emesis is not frequently encountered.

Intravenously, the dose of TEM is 0.05 mg./kg., never to exceed 5 mg. Doses of 0.25 mg./kg. intravenously are fatal in man. The oral dose is 0.1 to 0.3 mg./kg. TEM is available in 5-mg. tablets. The maximal oral daily dose seldom exceeds 5 mg.

The major hematologic toxic effects of TEM are similar to those elicited by Mechlorethamine, namely, *leukopenia*, *thrombocytopenia*, and less frequently, *anemia*.

The use of TEM in neoplastic disease is discussed by Rundles and Barton (1952). Many remissions under TEM therapy in malignant lymphoma have been dramatic. Results in chronic lymphocytic leukemia have also been encouraging.

TEM appears to offer distinct advantages over nitrogen mustard.

There are available other cytotoxic agents related to TEM which are used in the treatment of leukemia. One of these is *triethylenephosphoramide* (TEPA), which is administered intramuscularly, 0.3 mg./kg.; a course of treatment consists of 4 to 6 injections. Its side effects are similar to those of TEM; however, nausea and vomiting are rare (Farber *et al.*, 1953). Another agent is thio TEPA, in which a sulfur atom replaces the oxygen atom in the TEPA molecule. It is administered orally, 5 to 10 mg. daily, or intravenously, 0.2 mg./kg. It has been found useful in the treatment of chronic myelocytic leukemia and in the suppression of metastases of solid tumors (Shay *et al.*, 1953).

**Busulfan, U.S.P. (Myleran).** This compound was developed in the investigations of Haddow and Timmis (1953) in studying the tumor-inhibiting activity of sulfonic acid esters. The structure of busulfan is shown in the following formula.

$$CH_3 \cdot SO_2O \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OSO_2 \cdot CH_3$$

Busulfan, U.S.P.
Myleran
(1,4-dimethansulfonoxybutane)

Busulfan is a white crystalline powder; it is tasteless and insoluble in cold water.

**Pharmacologic response to busulfan.** The compound appears to evoke no other pharmacologic response except to depress *myelopoieses.* It is especially active on immature granulocytes. In mice, upon oral administration the $LD_{50}$ of busulfan was found to be between 150 and 200 mg./kg. Chronic feeding studies in rats showed that 240 mg./kg. per day was not injurious over a 6-month period. Higher dosage levels inhibited weight gain and cataract developed in about 10 weeks. These animals showed anemia, leukopenia, and thrombocytopenia. Neutrophils were replaced for the most part by lymphocytes.

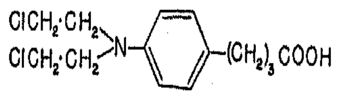
**Clinical use of busulfan.** Busulfan is indicated in the treatment of chronic *myelocytic leukemia.* Like other agents discussed, it is not curative but often provides control of the symptoms. When used in leukemia the response to busulfan differs from that of radiation or mechlorethamine in that a 50 per cent depression of the neutrophils may be produced without depression of the lymphocytes.

Busulfan has been studied critically in many clinics. The most promising results are achieved with the drug in myelocytic leukemia. For example, Galton and Till (1955) in their patients found 0.06 mg./kg. (about 4 mg. daily) to be the most satisfactory schedule for initial dosage. When remissions occurred the drug was discontinued for a period. They found that side effects were few, erratic responses were encountered only infrequently, and remissions were longer. Patients have been maintained on busulfan for more than 3 years. Galton favors radiation therapy also if it is available. He has found that patients who did not respond well to radiation have responded to busulfan therapy.

Haut *et al.* (1961) studied busulfan therapy in chronic myelocytic leukemia using long-term intermittent therapy. They administered 114 courses to 30 patients over 7 years. The major hazard of the therapy was pancytopenia, which was related to excessive doses. Morbidity was decreased and longevity (42 months median) was greater than that of previously reported untreated cases (31 months median) and appeared to be about equal to that achieved with $P^{32}$ and x-ray. Drug resistance in certain patients was encountered.

Under therapy with busulfan it is recommended that blood counts be made weekly. At the first sign of abnormal bone marrow depression the drug should be withdrawn or its dosage schedule promptly reduced. The absence of serious side effects and successful remissions with busulfan establish for it a place of prominence in the treatment of chronic myelogenous leukemia. Busulfan is available in 2-mg. scored tablets.

**Chlorambucil.** Chlorambucil or Leukeran is a derivative of nitrogen mustard synthesized by Everett *et al.* (1953). Its structure is shown in the formula.



Chlorambucil, Leukeran
[*p*-(di-2-chlorethylamino)phenylbutyric acid]

Chlorambucil occurs as a white crystalline powder which is very slightly soluble in water.

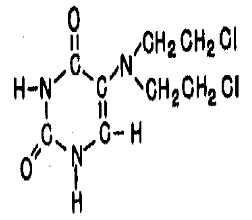
**Pharmacologic response to chlorambucil.** Haddow (1953) discovered that chlorambucil exhibited a pharmacologic action similar to nitrogen mustard. Chlorambucil inhibited the growth of Walker rat tumor 256. The oral absorption of chlorambucil is good. Single doses in rats of 12.5 mg./kg. elicit effects similar to those produced by nitrogen mustard. These include weight loss, atrophy of the intestinal mucous membrane and lymphoid organs, severe lymphopenia becoming maximal in 4 days, mild transient anemia, and thrombocytopenia. Rapid recovery usually follows. The approximate $LD_{50}$ of chlorambucil in rats upon intraperitoneal injection is 18.5 mg./kg. Death is preceded by convulsions.

**Clinical use of chlorambucil.** Chlorambucil is indicated in chronic lymphocytic leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease (Galton *et al.*, 1955). Chlorambucil is not curative but often provides remissions in a substantial segment of the cases. The management of leukemias with chlorambucil is more simple than with nitrogen mustard. The treatment is fraught with fewer side effects and is less damaging to the hematopoietic system. Excessive prolonged doses may produce severe bone marrow injury. During the administration of chlorambucil, weekly examinations of the blood are advisable.

Chlorambucil is available in sugar-coated tablets containing 2 mg. The daily dosage ranges between 4 and 10 mg. for 3 to 6 weeks. The total daily dose may be given at one time. Dosage should be reduced as soon as an abrupt fall in white cell count occurs. At present it is considered that short-course treatments are safer than continuous maintenance therapy. If the latter is used the dose should be held at 0.03 to 0.1 mg./kg., approximately 2 to 4 mg. daily. Chlorambucil appears to be relatively free from toxic effects other than its depressant action on the bone marrow. Gastrointestinal side effects, so frequently encountered with other derivatives of nitrogen mustard, are comparatively rare with chlorambucil. This compound is a welcome addition to our armamentarium of cytotoxic agents useful in the treatment of leukemia.

Rundles *et al.* (1959) found chlorambucil superior to busulfan in the treatment of chronic lymphocytic leukemia. However, in chronic granulocytic leukemia, busulfan was more effective than chlorambucil. They state, "Chlorambucil and busulfan appear to have relatively specific growth inhibitory effects on the lymphoid and myeloid tissues, respectively."

**Uracil Mustard.** One of the newer alkylating agents is uracil mustard. Its structure is shown in the formula:



Uracil Mustard
[5-(di-2-chloroethylamino) uracil]

Shanbrom *et al.* (1960) obtained objective improvement in 16 of 30 patients with Hodgkin's disease, 14 of 21 patients with chronic lymphocytic leukemia, and 11 of 13 patients suffering from chronic granulocytic leukemia. This amelioration of symptoms has been confirmed by Theologides and Kennedy (1962) in a series of leukemia patients.

The drug is administered orally in 1-mg. capsules and is well tolerated; the most common toxic manifestations are gastrointestinal. The dosage may vary from 1 to 5 mg. daily for several days to several weeks. Therapy is intermittent to avoid excessive depression of the hematopoietic system as well as excessive production of side effects.

**Demecolcin, Colcemide, Desacetylmethylcolchicine.** Demecolcin was mentioned on page 824 in its relationship to colchicine used in the treatment of gout. It evokes a marked depression in the leukocyte count and has been used in the treatment of leukemia. Lessmann and Sokal (1961) used the agent in 14 patients with chronic myelocytic leukemia. The drug proved to be as effective as other available agents and was remarkably prompt in its effects. The possible effectiveness against myeloblastic proliferation was noted. The duration of action was short and the margin of safety low. No gastrointestinal disturbance was observed. The most common side effect was hematologic depression.

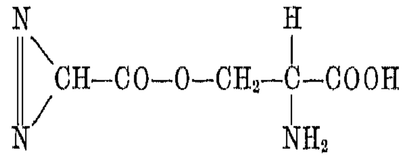
Initial dosage is 3 to 10 mg. daily and on occasion increased to 15 mg. daily. Management of the disease with Demecolcin seems to be more difficult than with other agents and its use appears to be quite limited. However, it is well to remember that it may be the means of extending life in patients in whom other drugs have been ineffective.

### ACTH AND ADRENOCORTICAL STEROIDS

ACTH and the adrenocortical steroids are capable of effecting remissions in leukemia. Their action is prompt, but the duration of the response is not as lasting as that achieved with the antimetabolites or cytotoxic agents. It has been established, however, that their concomitant use, especially with the folic acid antagonists in children, achieves a longer duration of life than the use of the antimetabolites alone.

### ANTIBIOTICS

**Azaserine (Sermyl).** Several antibiotics have been reported as eliciting antineoplastic activity. One of these is azaserine isolated from fermentation cultures of a species of *Streptomyces* identified as *S. fragilis*. The chemical structure of the compound is shown in the formula:



Azaserine

Azaserine is a light yellow-green crystalline powder which is soluble in water. The compound was synthesized by Moore *et al.* (1954) (page 104).

The activity of azaserine against microorganisms is not impressive. Stock *et al.* (1954) found azaserine to be active in inhibiting the growth of Crocker mouse sarcoma 180. Ellison *et al.* (1954) suggested the possible value of azaserine in acute leukemia. Alone in acute leukemia the drug appears now to be of little value. However, when used as adjunct therapy to mercaptopurine in acute leukemia the value of azaserine was manifested. For example, under mercaptopurine therapy complete remissions were seen in 44 per cent of the cases; with azaserine added in a similar series the remissions increased to 72 per cent (Karnofsky, 1955).

Azaserine is given orally, the dosage is 2.5 mg./kg. The only untoward effect noticed is that of *glossitis*.

**Urethane.** This compound is the ethyl ester of carbamic acid. It was used for many years as a mild hypnotic. It was observed that the use of large doses of the drug produced bone marrow depression. The drug was used for some time in the treatment of leukemia. It has now been replaced by more effective agents. For a discussion of its use the reader is referred to earlier editions of this text.

## DRUG-INDUCED BLOOD DYSCRASIAS

**Aplastic anemias.** These anemias are characterized by leukopenia, thrombopenia, hemorrhagic manifestations, absence of reticulocytes, nucleated erythrocytes, and polychromatophilic cells from the blood and marrow. The sternal marrow shows almost no nucleated cells. Aplastic anemia may result from the exposure to vapors of benzene, nitrobenzene, idiosyncratic reactions to organic arsenicals, and over-dosage with x-rays or radioactive substances. The removal of the incriminating agent is the first step in the treatment. Transfusion is given repeatedly in hope that the defective bone marrow might in the meantime assume again its normal functions. Generally the prognosis is grave.

**Agranulocytosis.** This is a deficiency of the granulocytes (polymorphonuclear leukocytes) in the circulating blood. This type of blood dyscrasia is produced occasionally by drugs used in the treatment of various diseases, such as aminopyrine and the sulfonamides (page 77). It is obvious from what has been said in the foregoing paragraphs and on page 735 that the target cells, affected by many drugs and industrial chemicals, lie in the bone marrow.

Furthermore, the "surprise" effect of urethane as a leukocytic depressant of the bone marrow made the compound available in the treatment of the leukemias. These facts should alert the vigilant physician in the administration of new drugs. He should realize that often bone marrow changes occur slowly, and frequent checks of the blood picture are but a reasonable precautionary measure, especially when treatment extends over long periods.

In figures 45-4, 45-5, and 45-6 are listed the drugs and the frequency and character of blood dyscrasia that may be produced. These data were reported by Erslev and Wintrobe (1962) from the Study Group on Blood Dyscrasias of the A. M. A. Council on Drugs since 1955. A total of 1195 cases has been reported where it was suspected that the blood disease was caused by drugs.

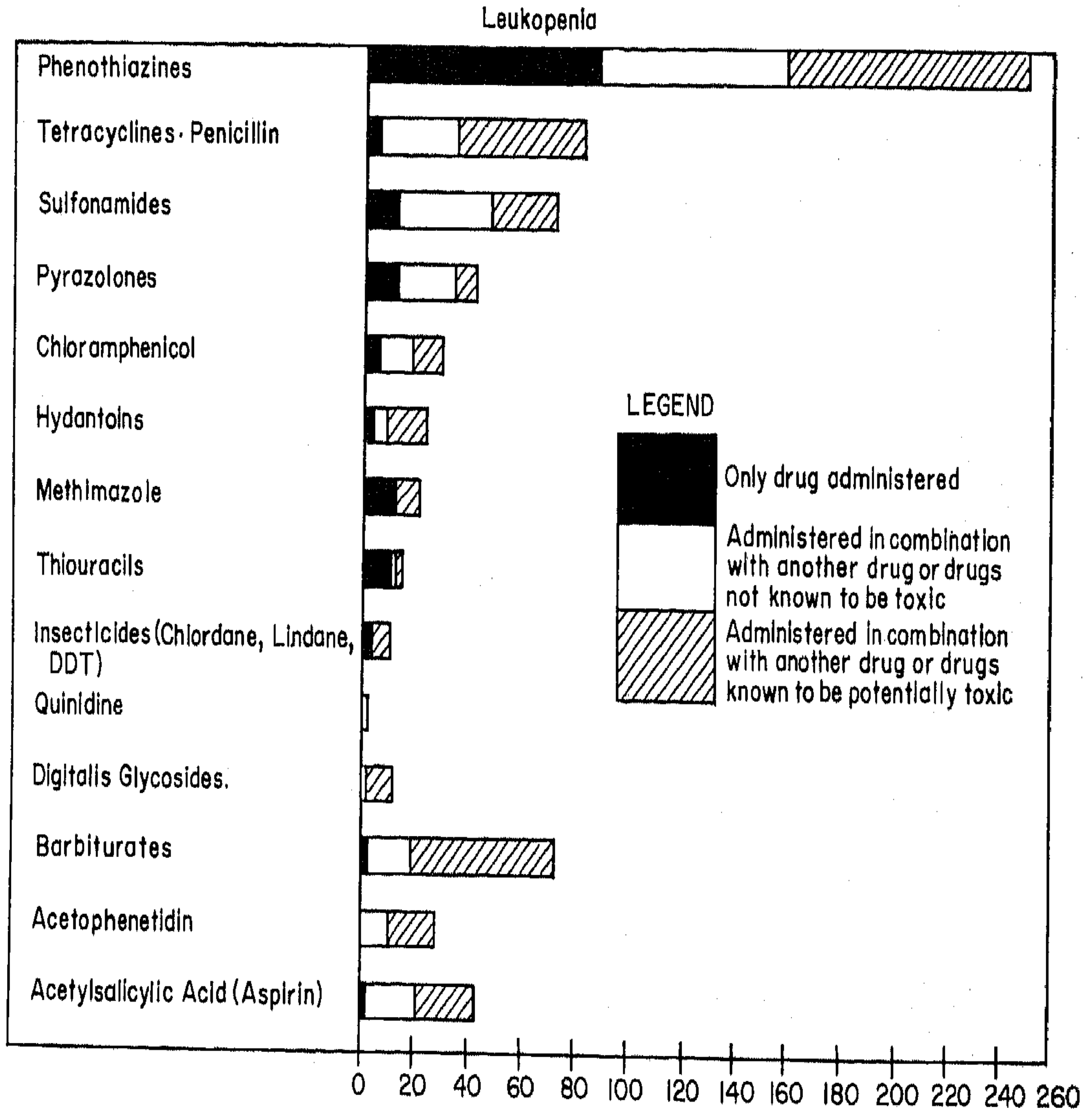


FIG. 45-4. Drugs commonly associated with the development of leukopenia

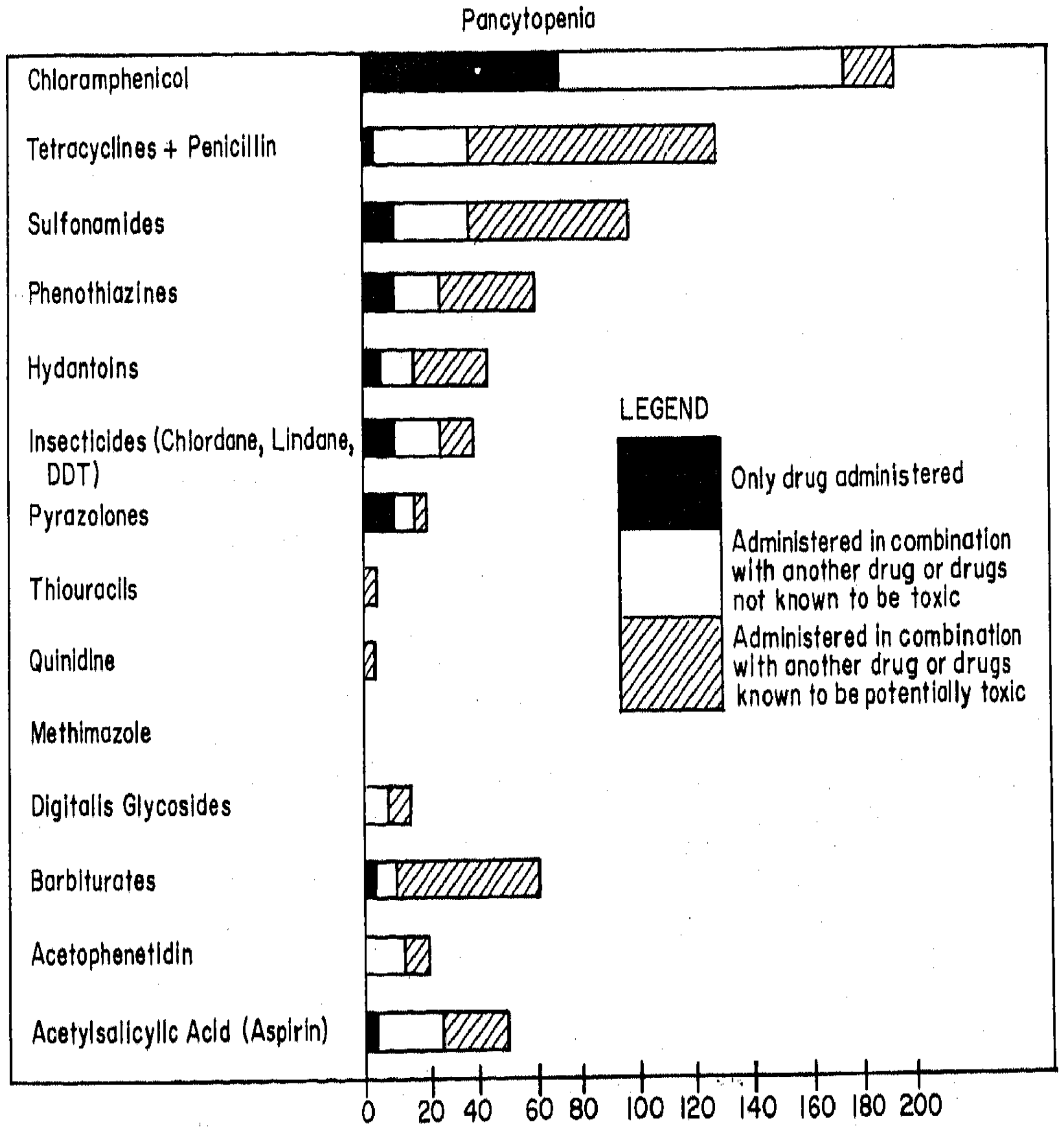


FIG. 45-5. Drugs commonly associated with the development of pancytopenia

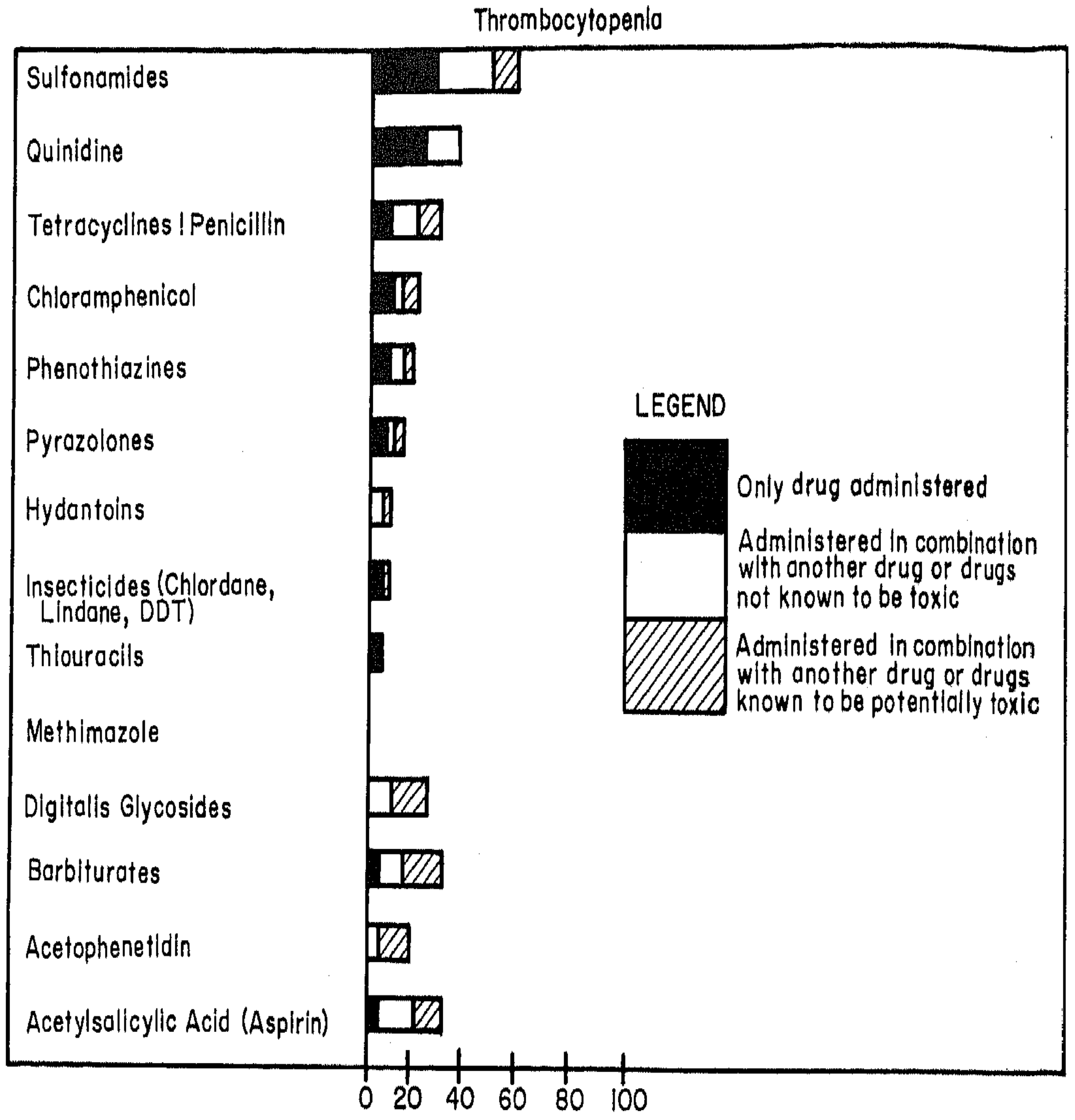


FIG. 45-6. Drugs commonly associated with the development of thrombocytopenia

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# PART VII

## THE PHARMACOLOGIC RESPONSE OF THE REPRODUCTIVE SYSTEM

## 46

## *The Response of the Uterus to Drugs*

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### Introduction

The uterus is an organ of paramount importance in the reproductive system of the mammal, whose chance of survival depends upon its proper functioning. The organ is capable of undergoing remarkable changes. For example, before pregnancy the organ may weigh about 50 gm. and during the course of gestation its weight may increase to 1000 gm. During this period its capacity may change from 5 ml. to 5 L.

The *myometrium*, or the muscular layer of the uterus, is very thick. It is composed of smooth muscle. There are an inner circular layer and outer layers of longitudinal and oblique muscle fibers. The myometrium is very vascular. The blood vessels run between the interstices of the muscle fibers. Because of this arrangement, when the empty uterus contracts the blood vessels are clamped or squeezed in many areas, and bleeding is controlled.

The uterine muscle undergoes spontaneous rhythmic contractions. These occur *in situ*, and when the organ is excised and placed under the proper conditions in a smooth muscle chamber these movements continue for long periods of time. The uterine contractions *in situ* are similar to peristaltic waves. They originate in the fallopian tubes, pass down the tubes to the uterus, and here excite muscle contractions. The force and frequency of the uterine contractions are dependent upon many different factors. Among these are the period of the menstrual cycle and whether or not the uterus is gravid. The virgin uterus shows only mild contractions except just prior to menstruation. The contractions of the gravid uterus are weak during the early months of pregnancy. However, as term approaches the contractions become more frequent and forceful.

The contractions of the uterine muscle do not appear to be correlated by a local plexus, like the intestinal movements. The activity of the organ continues after the severance of its autonomic nerve supply.

Like other smooth muscle the *myometrium* is innervated with sympathetic nerves. Both motor and relaxant fibers to the uterus are sympathetic in character in the human being. There is, however, wide species variation in uterine innervation. The sympathetic nerves to the uterus originate from the first, second, and third lumbar roots. They pass through the inferior mesenteric ganglion and the hypogastric nerves to the uterus. These sympathetic nerves contain cholinergic fibers, and the human uterus is contracted by acetylcholine and pilocarpine and relaxed by atropine.

### Methods of Study of the Action of Drugs on the Uterus

It has been stated previously that the innervation of the uterus enjoys a wide species variation. It follows therefore that the action of adrenergic and cholinergic stimulants and depressants on the uteri of various species would be subject to a similar variation. This is indeed true, and in former years much of our knowledge with regard to the action of drugs on the human was obtained by animal experiment. These data were extrapolated to the human being and many times were misleading. For example, epinephrine relaxes the smooth muscle preparation of the rat's gravid or nongravid uterus. The same drug stimulates the force of contraction of the pregnant or nonpregnant rabbit's uterus. But in the cat, the gravid uterus is contracted by epinephrine, and the nongravid organ is relaxed. At term the human uterus appears to be relaxed by epinephrine.

If a drug is to be tested for its action on the uterus of a laboratory animal, more dependable results are achieved by conducting the test *in situ* than on a smooth muscle preparation of the uterus *in vitro*. The uterus of the guinea pig or other suitable laboratory animal is exteriorized through an abdominal incision into the anesthetized animal. The organ is attached to a writing lever and tracings are obtained in the usual manner. The drug is injected intravenously and thus reaches the organ through the circulation. This technic resembles the clinical use of the drug. On the other hand, allowing the drug to come in direct contact with the organ in the smooth muscle chamber is likely to produce results which do not serve as a reliable indication of the action of the drug on the uterus when it is administered orally or parenterally. The relaxant action of an aqueous extract of corpus luteum parenterally on the uterus of the virgin guinea pig is shown in figure 46-1 (Krantz, Bryant, and Carr, 1950).

A smooth muscle preparation of a human uterine strip is an excellent test object to ascertain a first approximation of the action of drugs on the human uterus. When the organ is removed surgically because of the presence of fibroid tumors, the muscular strips free from tumor tissue are used as a smooth muscle preparation. If it is the object of the experiment to ascertain the action of a drug on the uterus at term, a uterine strip may be obtained from a cesarean section and used in the muscle chamber.

Another procedure which may be employed in animals or in the human being is to fill the uterine cavity with a fat containing iodine. The heavy iodine atoms are opaque to x-rays, and the outline of the uterus thus becomes visible roentgenologically. The contractions of the organ can be followed after drug administration by further x-ray studies.

The use of a uterine balloon distended within

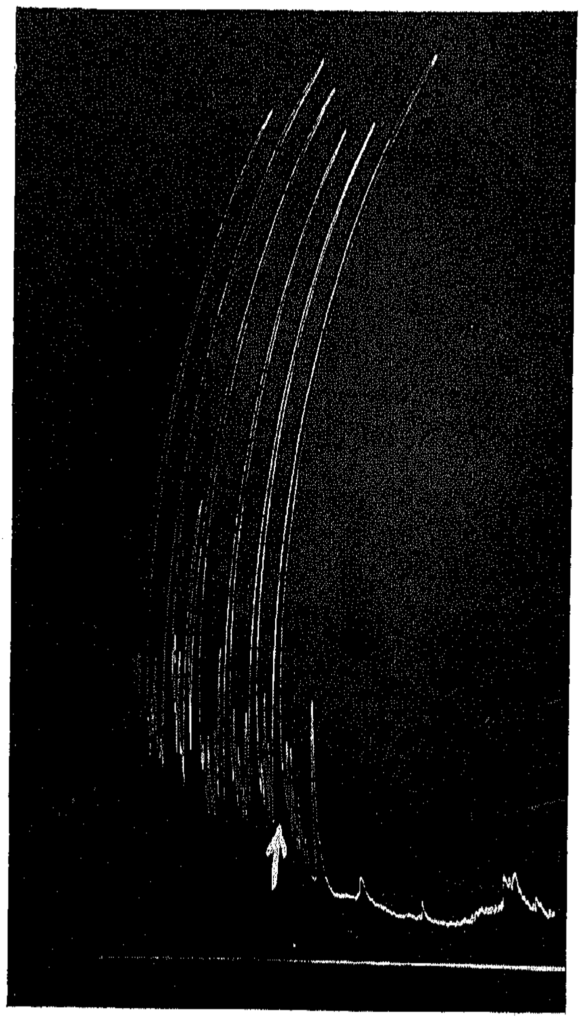


FIG. 46-1. Relaxation of guinea pig's uterus *in situ*. (From J. C. Krantz, Jr., H. H. Bryant, and C. J. Carr, Surg. Gynec. & Obst., 90: 372, 1950.) Action of aqueous corpus luteum on the guinea pig's uterus. (Intravenous injection, 2 ml./kg, at the *arrow*.)

the organ appears to be one of the most physiologic and satisfactory methods of studying the action of drugs on the uterus. It is available in animals and in the human being. Besides, it may be used in the nongravid or in the gravid uterus. The balloon may be filled with fluid or air. The contractions of the myometrium cause the balloon to diminish in size, increasing the pressure in the system, which is recorded. An illustration of the action of ergonovine on the human uterus *in situ* is shown in figure 46-3.

Mendez-Bauer *et al.* (1960) used a strip of mammary gland from a lactating rabbit as a smooth muscle preparation to assay the uterine potency of oxytocin preparations. The contractions of the strip are recorded isometrically. The strip shows no spontaneous contractions, but responds with reasonable linearity and stability to oxytocin at concentrations ranging from 0.5 to 10 mU./ml. Assays *in vitro* of this character are very useful and reliable in evaluating the potency of oxytocic drugs for human use, especially when a standard preparation is available for comparison.

Probably the most accurate method of testing the effect of drugs upon the human uterus *in vivo* is by means of the *multichannel tokodynamometer*.

In addition to giving consideration to the action of drugs on the uterine musculature at the time of delivery, we will discuss the action of agents which afford relief in dysmenorrhea in another chapter. In a subsequent chapter the hormonal control of the uterus will be considered.

### ACTION OF ERGOT ON THE UTERUS

**The nature and history of ergot.** Ergot results from a fungus infestation of rye. For many years ergot was regarded simply as diseased rye. Toward the end of the eighteenth century the disease was recognized as an attack of fungus. The fungus is prevalent in grain fields, especially in moist, warm weather. Its spores are carried by wind or insects to the young ovaries of the rye. In the ovary the spores germinate into hyphal filaments, which secrete a ferment and so penetrate the basal portion of the ovary. The tissue of the grain is decomposed by the ferment, with the formation of a yellow, viscid substance called *honey-dew*. This attracts insects which in turn spread the fungus to other spikes of rye. The hyphal filaments penetrate deeper into the ovary, and the latter disappears, being replaced by a hardened, curved, purple body called the *sclerotium* or *ergot of rye*. This sclerotium which replaces the grain of rye is the official ergot.

There is evidence that ergot was probably used by midwives of France in the eighteenth century. Paintings of the lying-in chambers of this era depict the midwife preparing an herbal decoction. It was in all probability ergot.

Madam Dupille of Chaumont wrote to a Parisian apothecary in 1774 and stated that in her practice as a midwife she was using a thimbleful of powdered ergot to hasten labor. This, however, she used only in those women having favorable presentations.

In 1777 a physician named Desgranges met a midwife in Lyons who was using ground ergot in her practice. Desgranges became interested in the drug and later used it repeatedly in delivery. He called it *Poudre Obstétricale*.

Knowledge of the use of ergot spread to Holland and America, and in 1808 a letter appearing in the Medical Repository of New York bore the title "Account of Pulvis Parturiens, a Remedy for Quickening Child-birth." In America, ergot preparations of the early nineteenth century were made extemporaneously by boiling water containing a teaspoonful of powdered ergot. The aqueous extract was then employed. These potions were nauseating but very effective, although not always dependable.

Toward the latter part of the nineteenth century the galenical preparations of ergot became established. There was a wine, a dry extract, and the fluidextract. The fluidextract of ergot remained the ergot preparation of choice until 1936, when the alkaloid *ergonovine* was isolated from the drug. *Ergotoxine* had been obtained from ergot in 1906, but its action in obstetrical practice did not completely replace the extractive preparations of ergot.

**Chronic ergotism.** Ergotized rye is a toxic substance. Peasants in Spain and Russia, where a great deal of rye is grown, often suffered from chronic ergot poisoning. In the middle ages the people of Europe often associated their numerous plagues and epidemics to the *failure of the crops* and the presence of *swarms of insects*. Mezeray, in his history of France, describes epidemics of ergotism in 944 and 1090. He assigned the name *St. Anthony's Fire* to the epidemic.

Ergotism took its greatest toll among the peasant classes. They ate the poor grade of rye flour which had been attacked by the fungus. Historians of the period described the poisoning as of 2 kinds, the gangrenous and the convulsive type. The gangrenous type was prevalent in France, west of the Rhine River. The convulsive type prevailed in Russia and in the territory east of the Rhine. It is difficult to speculate as to why these types of ergotism appear to be geographically divided. Mellanby (1930) suggested that the prevalence of the severe type of convulsive ergotism of Germany and Russia was aggravated by a basic vitamin A deficiency in the diet of these peoples. In France this deficiency did not obtain, and the ergotism which occurred became the chronic gangrenous type.

The gangrenous type of ergotism affected the hands and feet. Vascular stasis caused drying and mortification of the tissues. The dead, dried joints would break off without bleeding. In the acute convulsive type of ergot poisoning, the patient suffers from periodic convulsive seizures of the extremities and often of the trunk itself. The pain is excruciating. Loraine, in 1805, mentioned the fire or burning sensation as being "holy." He states: "Many were tortured and twisted by a contraction of the nerves; others died miserably, their limbs eaten up by the holy fire and blackened like charcoal." From frescoes of Europe in the middle ages, we see that St. Anthony was the saint to whom the individual suffering with ergotism pleaded for succor.

Fitzhugh *et al.* (1944) studied the effect of chronic ergot poisoning in the rat. Concentrations of 1, 2, and 5 per cent of ergot in the diet showed toxic effects. Growth was retarded. Of interest is the fact that at the 5 per cent level there was a high incidence of neurofibromas on the ears of the animals.

Cases of ergotism today are rare. Improved agricultural procedures and a generalized alerting of peasants to the dangers of ergotized rye have nearly obliterated the epidemics. They are of historical interest and also of interest because the symptoms of ergotism will be observed to some extent in our study of the pharmacologic actions of ergot.

**The constituents of ergot.** Wenzell (1864) was the first to show that ergot contained alkaloids. The first alkaloid isolated from ergot was *ergotinine*. In 1906 Barger *et al.* isolated *ergotoxine*. Spiro and Stoll (1920) isolated *ergotamine* and *ergotaminine*. The drug proved to be a veritable "treasure house" of alkaloids, and further investigations yielded *sensibamine* (Kereszty and Wolf, 1933) and *ergoclavine* (Küssner, 1934).

Despite the fact that these various alkaloids of ergot had been isolated, the extractive preparations of ergot remained very popular. Foremost among these was the fluidextract. This was made with a hydroalcoholic menstruum and contained the alcohol-soluble ergotoxine. Nevertheless, it was recognized by clinicians that aqueous extracts of ergot were potent in their action upon the uterus. These extracts contained little ergotoxine, and yet their uterine action was more persistent than that of ergotoxine or the fluidextract which contained the alcohol-soluble alkaloid. It appeared therefore that aqueous extracts of ergot contained a principle, not present in the fluidextract to any appreciable extent, which elicited the prolonged uterine action desirable in obstetrics.

Almost simultaneously 4 independent investigations led to the isolation of this alkaloid. Kharasch and Legault (1935) called the new substance *ergotocine*. Dudley and Moir of England (1935) named the new alkaloid *ergometrine*. Thompson (1935) designated the alkaloid first as *alkaloid X* and then assigned the name *ergostetrine*. Stoll and Burckhardt (1935) of Switzerland isolated the alkaloid and named it *ergobasine*. It was soon demonstrated by Chen *et al.* (1936) that the 4 products isolated from ergot were identical, and the name *ergonovine* was assigned to the alkaloid.

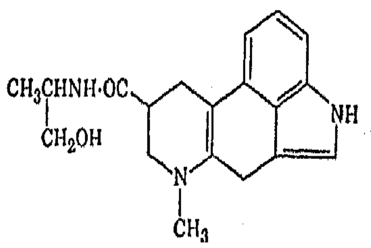
Ergonovine elicits the therapeutic uterine response of ergot and its preparations. It is a chemical entity which is stable and dependable; therefore the use of extractive preparations of ergot has become outmoded. The crude drug ergot has been thoroughly investigated by the chemist, and the principal constituents may be divided into 2 classes: first, alkaloids, and second, amines and other nitrogenous compounds. These are as follows:

CONSTITUENTS OF ERGOT

| *Alkaloids* | *Amines and Other Nitrogenous Compounds* |
|---|---|
| 1. Ergotamine group | Acetylcholine |
| Ergotamine | Choline |
| Ergotaminine | Histamine |
| Ergosine | Tyramine |
| Ergosinine | Trimethylamine |
| 2. Ergotoxine group | Isoamylamine |
| Ergocristine | Secale amino sulfonic acid |
| Ergocristinine | Putrescine |
| Ergokryptine | Cadaverine |
| Ergokryptinine | Agmatine |
| Ergocornine | Betaine |
| Ergocorninine | Uracil |
| 3. Ergobasine group | Vernine |
| Ergobasine (Ergonovine) | Guanosine |
| Ergobasinine | Ergothioneine |

Clinically, 2 of the alkaloids are important They are *ergotamine*, (action similar to ergotoxine), which has been discussed on page 562, and *ergonovine.*

**Chemistry of ergonovine.** The alkaloids of ergot are derivatives of lysergic acid. The structure of ergonovine is shown in the formula.



Ergonovine
(Ergonovine is the amide of lysergic acid with *d*-2-aminopropanol)

Stoll (1950) showed that the degradation products of ergonovine are *d*-2-aminopropanol and lysergic acid. It is of interest to note that the 2-aminopropanol grouping of ergonovine (derived from the amino acid α-alanine) is in the *d*-form. This represents an unusual configuration not generally found in natural products.

**Ergonovine Maleate, U.S.P.** This product is the maleate of the principal uterine alkaloid obtained from ergot. It is a white or faintly yellow, microcrystalline powder; 1 gm. of the alkaloidal salt is soluble in 36 ml. of water. Ergonovine has now been synthesized (Kornfeld *et al.*, 1954), but the naturally-occurring alkaloid extracted from ergot still represents the source of the approximately 12 kg. of ergonovine used annually in the United States.

## PHARMACOLOGIC RESPONSES TO ERGONOVINE

**Action on the uterus.** Ergonovine produces prompt and powerful contractions of the human uterus and the uteri of many other species. The response in the human being is promptly evoked by the intravenous, intramuscular, or oral administration of the drug. The action also may be readily observed on smooth muscle preparations from the human uterus.

The action of ergonovine on the human postpartum uterus may be observed in figure 46-2.

The drug upon injection causes the uterine muscle wall to contract firmly. The myometrium becomes blanched, and the muscle shows marked tetanus, as illustrated in the tracings.

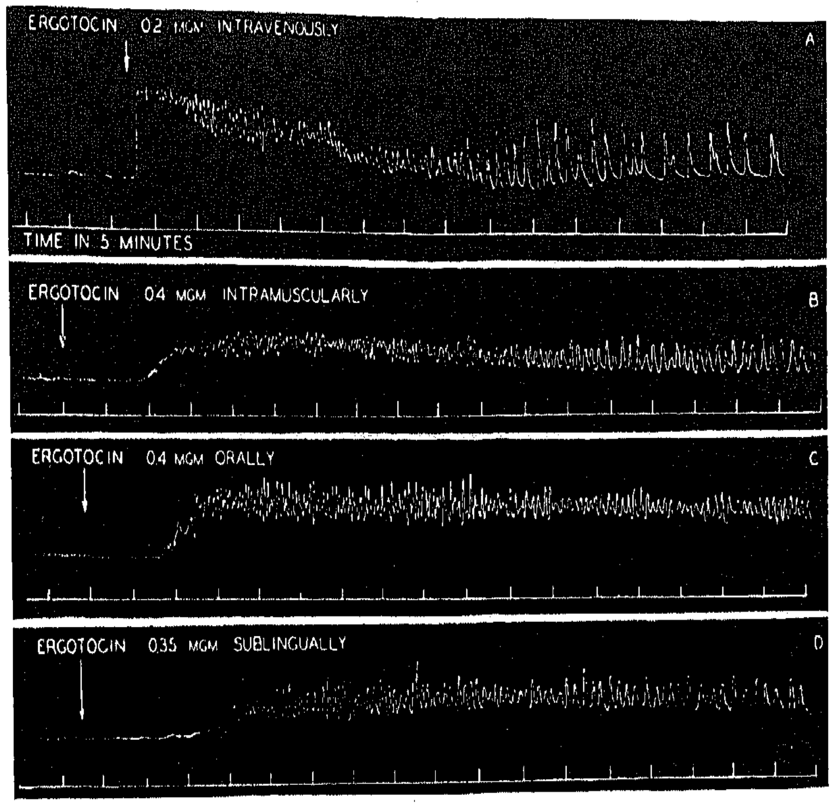


FIG. 46-2. Action of ergonovine on human postpartum uteri. *A*, Subject M. K., para 3, postpartum day 6; *B*, Subject M. O., para 3, postpartum day 8; *C*, Subject E. G., para 2, postpartum day 6; *D*, Subject R. P., para 2, postpartum day 7. (From M. E. Davis, F. L. Adair, K. K. Chen, and E. E. Swanson, Jr. Pharmacol. & Exper. Therap., **54**: 398, 1935.)

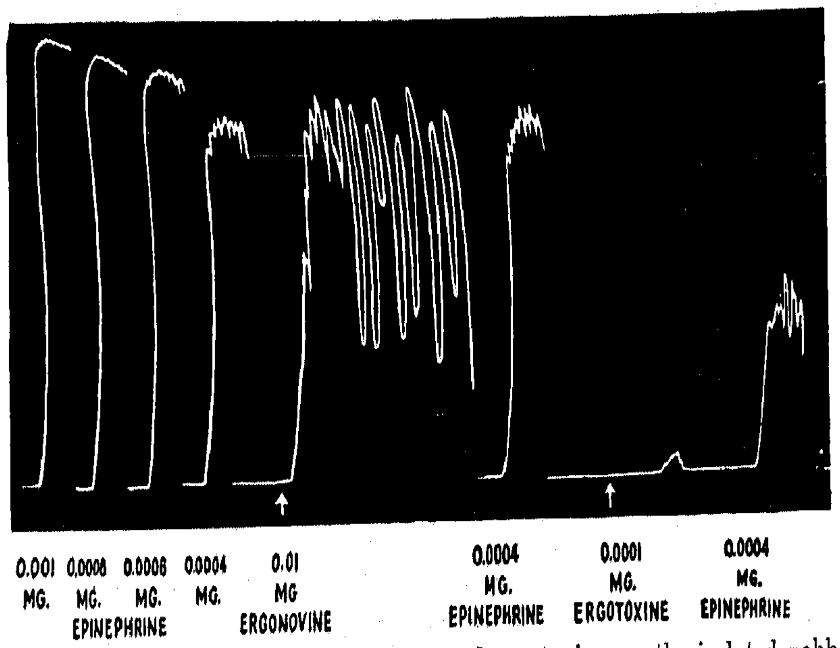


FIG. 46-3. The effect of ergonovine, epinephrine, and ergotoxine on the isolated rabbit's uterus. (Chen, 1946)

On the isolated uterus of the rabbit which is not stimulated by ergotoxine, ergonovine produces prolonged rhythmic contractions (fig. 46-3). It also increases the uterine tonus. This action is produced with dilutions as high as 1:2,000,000 (Davis *et al.*, 1935). In this respect ergonovine resembles the action of epinephrine on the rabbit's uterus.

The isolated uterus of the guinea pig is also contracted by ergonovine. This tissue is even more sensitive to the drug than the rabbit's uterus

The estrogens sensitize the uterus to the action of ergonovine, and progesterone renders the myometrium less sensitive to the action of the drug.

**Action on the cock's comb.** Ergot and its preparations produce cyanosis in the comb of the white Leghorn rooster. This action has been used for years as an indication of the activity of various crude ergot products. Indeed, the action formed the basis of the official ergot assay for many years. The 2 principal alkaloids of ergot, ergonovine and ergotoxine, elicit this response. Therefore, the degree of cyanosis produced by a crude ergot preparation serves as a first approximation of the active alkaloidal content of the drug.

This action of the ergot alkaloids on the peripheral circulation (cock's comb) is comparable to the incipient stage of ergotism discussed on page 749. The drug produces thrombosis of the small arterioles. Definite injury is seen in the capillary endothelium. Blood corpuscles block capillary flow, and a vascular stasis results. Although no histologic changes are found in the blood vessels of the cock's comb in the acute cyanosis, repeated injections of ergot preparations or ergotoxine will cause the condition to progress to dry gangrene. The effect of ergonovine is milder and apparently does not produce progressive anatomic changes that result in gangrene (Davis *et al.*, 1935). Thus, when the alkaloids of ergot are given repeatedly, as in the treatment of migraine (see page 566), there is less danger of ergotism from the use of ergonovine than from ergotoxine (ergotamine).

**Action on the circulation and respiration.** In cats and dogs under ether anesthesia, 0.1 to 0.5 mg. of ergonovine intravenously produced no significant changes in blood pressure. Larger doses of the alkaloid (1 to 30 mg.) produced a fall in blood pressure in cats. The depressor response was not blocked by the previous administration of atropine. Perfusion of the frog's heart *in situ* with a solution of ergonovine 1:10,000 caused a decrease in ventricular rate with a diminution of systole and diastole (Davis *et al.*, 1935).

Respiratory rate and volume were depressed in the etherized cat by the intravenous injection of from 5 to 30 mg. of the alkaloid. The resulting hypoxia produced cyanosis and circulatory depression. Davis *et al.* (1935) report that invariably artificial respiration relieved the respiratory embarrassment.

**Effect on smooth muscle.** Solutions of ergonovine maleate, 0.5 per cent, instilled into the conjunctival sac of the rabbit produce pupillary dilatation. The light reflex is preserved. This response is similar to that produced by the sympathomimetic amines such as ephedrine and is therefore suggestive of sympathetic stimulation.

The leg vessels of the frog (Trendelenberg experiment) are constricted by solutions of ergonovine maleate in dilutions of from 1:50,000 to 1:150,000. This action also is shared by epinephrine.

The intestine of the rabbit, which is relaxed by epinephrine, is relaxed also by ergonovine. Ergotamine abolishes the action of ergonovine on the rabbit's intestine.

Judging from the action of ergonovine on various smooth muscle structures, it appears that the drug emulates certain of the responses elicited by epinephrine and many of the sympathomimetic amines. The oxytocic action of the alkaloid is likely to be associated with its capacity to effect sympathetic stimulation. There is also a powerful direct musculotropic component in the action of the drug on the uterus (Davis *et al.*, 1935).

**Effect on metabolism.** When rats are injected intravenously with solutions of ergonovine maleate, 5 mg./kg., the basal metabolic rate is increased approximately 32 per cent. This action of ergonovine is also produced by epinephrine (see page 545). However, epinephrine is a far more potent stimulator of oxygen consumption than is ergonovine.

**Toxicity.** Ergonovine is one of the most powerful of all of the vegetable alkaloids used in therapeutics. In obstetrical practice the substance is administered only for short periods of time. If used in the treatment of migraine, the drug is given repeatedly. Davis *et al.* (1935) found the minimal lethal dose of the alkaloid administered intravenously to mice to be 250 mg./kg. In mice and guinea pigs the terminal symptoms were erection of the hair, dragging of the hind legs, periodic clonic convulsions, and death.

Two dogs were given daily 0.5 and 1 mg./kg., respectively, of ergonovine maleate by intravenous injection. A transient proteinuria was produced in the animal with the larger dosage. It disappeared when the drug was discontinued. The dog receiving the smaller dose showed no abnormalities that could be attributed to the administration of the drug.

**Therapeutic use.** *The principal use of ergonovine is to check postpartum bleeding.* For this purpose the drug may be administered intravenously, intramuscularly, or orally; the parenteral dose is 0.2 mg. and the oral dose is 0.5 mg. For postpartum hemorrhage the drug is used intravenously to insure promptness of action.

To prevent postpartum bleeding, ergonovine may be given orally; however, the parenteral use is not contraindicated. The drug should not be given before the baby is out of the uterus. Ergonovine may be administered before the placenta is expelled (Greenhill, 1960). These authors especially recommend the use of ergonovine in cases of *prolonged* or *instrumental labor* and in cases of *placenta praevia* and *abruptio placentae.*

Ergonovine is used in cases of incomplete abortion. It hastens the uterine expulsion of the products of conception and diminishes bleeding. For this purpose 0.2 mg. is given 4 times a day for a period of 4 days.

Ergot preparations should never be given during the course of pregnancy, nor should they be administered during the first or second stages of labor. Their principal use is to check postpartum bleeding by obliterating open sinuses after the expulsion of the placenta. Greenhill (1960) states, "However, ergonovine may be given without much risk even before the placenta is expelled."

When labor is conducted under saddle block, caudal, or local infiltration anesthesia, *i.e.*, under any but inhalation anesthesia, the giving of ergonovine by the intravenous route may be followed by a sudden rise in blood pressure, which occasionally reaches alarming heights. A minor degree of the hypertensive effect may be observed after intramuscular use of the drug. Because of the greater degree of hypertensive response from ergonovine than from Methergine (methylergonovine tartrate), the latter drug is preferred, especially in cases of pre-existing hypertension.

Pitocin given intravenously under the same circumstances may produce a minor rise in blood pressure.

When the delivery is carried out under saddle block or caudal anesthesia, the use of these drugs as a prophylactic is contraindicated. If hemorrhage as the result of uterine atony occurs, either may be given with safety and is remarkably efficacious.

**Methylergonovine Maleate, N.F. (Methergine).** Methergine is a synthetic derivative of ergonovine. It contains an additional methyl group on the alkyl side chain. The action and use of Methergine are similar to those of ergonovine. Its adrenergic activity is less than that of ergonovine. When assayed against ergonovine on the isolated uterus, Methergine is 1½ times more potent. Besides, its action is more prompt and of longer duration.

Shade (1951) employed Methergine in 200 patients postpartum. Only 11 per cent showed a significant rise in blood pressure from the drug. A control group of the same number received ergonovine. In this series significant elevations in blood pressure occurred in 29.5 per cent. Bunch (1948), in a series of 130 cases, quantitatively found less uterine bleeding after delivery when Methergine was used than when ergonovine was employed as the oxytocic.

It does appear from an ever-increasing number of comparative studies on the value of Methergine and ergonovine that Methergine is gaining in favor. With regard to the problem of blood loss at delivery, the advantage of Methergine is still polemic. However, one is inclined to believe that Methergine is as useful as ergonovine, and possibly somewhat superior, in curtailing blood loss (Eastman, 1957).

Forster (1957) studied the effect of the 2 drugs on the elevation of blood pressure in over 4000 deliveries. He confirmed the observation of Shade (1951) that ergonovine more frequently caused a rise in blood pressure than did Methergine. Pressure effects of significant magnitude with either drug are more likely to be evoked in hypertensive women than in those with normal blood pressure. In reviewing this problem, Eastman (1957) stated, "In our own clinic (Johns Hopkins Hospital) we switched several years ago from ergonovine to Methergine and feel that this change was advantageous because blood pressure rises and other unfavorable effects seem to be definitely less with Methergine than we formerly experienced with ergonovine."

Methergine is used in the same manner as is ergonovine. The dose of Methergine is 0.2 mg. intravenously or intramuscularly. It is also available orally in tablets of 0.2 mg.

### ACTION OF POSTERIOR PITUITARY INJECTION ON THE UTERUS

The *hypophysis cerebri,* or *pituitary body,* is a complex structure with important physiologic functions. Structurally it may be divided into 4 components: the *pars anterior,* the *pars intermedia,* the *pars nervosa,* and the *pars tuberalis.* From the standpoint of its physiologic functions and the pharmacologic response of its extracts, the gland may be conveniently divided into the anterior lobe (pars anterior) and the posterior lobe, which embraces the pars intermedia and pars nervosa. Hormones elaborated by the anterior lobe and posterior lobe of the pituitary gland exhibit marked pharmacologic responses. The special interest in this chapter is in the extracts obtained from the posterior lobe of the pituitary body.

**Historical background on posterior pituitary.** Oliver and Schaefer (1895) were the first to make the observation that extracts of the pituitary gland, when injected into animals, evoked a pressor response. Howell (1898) demonstrated that the pressor substance was present in the posterior lobe. The use of posterior pituitary extracts was introduced into obstetrical practice in 1909. Abel and Kubota (1919), through a series of brilliant researches, separated histamine, which is active in producing uterine contractions, from posterior pituitary extracts. Later these investigators succeeded in obtaining the oxytocic substance in the form of a tartrate which was at least 1000 times more active on the uterus than histamine.

Abel's tartrate combination of the pituitary principles elicited at least 4 specific pharmacologic responses, as follows:

1. Marked oxytocic action
2. Prolonged rise in arterial pressure
3. Brief diuresis in the rabbit
4. An antidiuretic action in diabetes insipidus

The substance obtained by Abel evoked the 3 principal actions of posterior pituitary preparations, namely, the *uterine response*, the *pressor action*, and the *antidiuretic activity* in diabetes insipidus. Abel (1930) held tenaciously to the view that there was one principle ("unitarian principle") responsible for the chief actions of the pituitary preparations.

Kamm *et al.* (1928) succeeded in separating the pressor and oxytocic principles of the posterior lobe of the pituitary body. Starting with dry posterior pituitary powder, which elicits both pressor and oxytocic responses, they obtained the oxytocic principle (*Pitocin*) and the pressor principle (*Pitressin*). Pitocin exhibited 150 times the activity of the original powder and was quite devoid of pressor response. Pitressin showed a pressor action 80 times greater than that of the posterior pituitary powder. It had little activity of the uterus. Electroendosmosis studies by du Vigneaud *et al.* have shown that the pressor and oxytocic principles are separate and distinct substances, as they enjoy different degrees of fugacity when subjected to electroendosmosis.

The 2 principles appear to be polypeptides. Du Vigneaud *et al.* (1953a) showed that high-potency oxytocin preparations of known composition migrate as a single electrophoretic component. Beef vasopressin migrated as a single biologically active component containing pressor, antidiuretic, and oxytocic activities. The ratio of the 3 activities in the beef vasopressin was 7.5:7.5:1.

Du Vigneaud *et al.* (1953b) found that highly purified preparations of oxytocin upon hydrolysis yielded 1 equivalent each of leucine, isoleucine, tyrosine, proline, glutamic acid, aspartic acid, glycine, and cystine, and 3 equivalents of ammonia. The active principle appeared to be a polypeptide of approximately 1000 molecular weight. Degradative studies indicated some type of cyclic disulfide. On the basis of further degradative studies, a structure was postulated for oxytocin. The compound was synthesized.

Du Vigneaud states:

> "The material in the peak tube (counter-current distribution) was not distinguishable in potency from one of our best preparations of natural oxytocin when these were assayed repeatedly against one another (i.e., by the chicken depressor method).
>
> "The synthetic material possessed the expected oxytocic activity in the isolated rat uterus. Furthermore, the synthetic product was fully effective in stimulating labor in the human. The synthetic material likewise possessed milk-ejecting activity in the human; approximately 1 µg. of either the synthetic or natural material given intravenously to patients induced milk ejection in 20 to 30 seconds.
>
> "If the synthetic product truly represents oxytocin, which it does in so far as we have been able to ascertain, this would constitute the first synthesis of a polypeptide hormone. What effect slight changes in the structure of a compound of such complexity might have on chemical, physical and biological properties must be investigated."

The molecules of oxytocin and vasopressin were found to differ but slightly in their chemical constitutions.

The synthetic oxytocic principle is now available under the name of *Syntocinon*. Its oxytocic activity *in situ* and *in vitro* coincides with that of the natural oxytocin. Nixon and Smyth (1957) compared Syntocinon with natural purified oxytocin in about 60 cases (postpartum) clinically. Within the limits of accuracy of their clinical observations they were unable to detect any significant difference in the oxytocic action or side effects of the two agents when administered intravenously in doses up to 1 unit. They state, "The postpartum series shows that the two drugs are practically identical."

The principle that is elaborated by the pars intermedia has been called *intermedin*. It elicits no specific pharmacologic or known physiologic action in man. Its principal action is seen in lower vertebrates, where it causes an expansion of the melanophores in the skin. This substance is distinct from the pressor and oxytocic principles.

In the pituitary gland the oxytocic activity is protein-linked (Lindner *et al.*, 1959). Smith and Rosenfeld (1962), using chromatographic analysis of the dialyzed pressed juice, observed 3 distinct zones of oxytocic activity: peak "1," representing 80 to 90 per cent of the activity filtered at a slow rate of high molecular weight protein; peak "2," filtered at the same rate as synthetic oxytocin; and peak "3," exhibiting an intermediate filtration rate. This product appears to be an intermediate between the protein complex of the octapeptide oxytocin and the free oxytocin. Smith and Rosenfeld suggest that this component might serve as an intermediate in one of the pathways concerned in synthesis, transport from the hypothalamic centers, or release of the hormone into the blood stream.

**Posterior Pituitary Injection, U.S.P.** This injection contains the pressor and oxytocic principles. *Oxytocin Injection, U.S.P.* (*Pitocin*) is a solution of the oxytocic principle. Its advantage is obvious from the viewpoint of obstetrical practice. The specific action is uterine and is not complicated by a rise in blood pressure or other concomitant actions. Another advantage of oxytocin over the whole posterior pituitary extract is the fact that the former may be given intravenously without risk of anaphylactic reaction, while the latter must be used intramuscularly if injected. The discussion in this chapter will be confined to oxytocin. Under the heading of diabetes insipidus, the action of vasopressin will be discussed (see page 815).

**Action of oxytocin on the uterus.** Oxytocin solution is an aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland. The product contains little pressor activity. The solution contains the equivalent of 10 posterior pituitary U.S.P. units/ml.; 1 unit is equivalent to the activity of 0.5 mg. of U.S.P. Posterior Pituitary Reference Standard. The product is standardized by testing its activity on the blood pressure of the anesthetized chicken. In this animal the injection elicits a precipitous, evanescent depressor response. The assay has been exhaustively studied by various investigators. Stewart (1950) in England reviewed the previous work and presented data to show that the depressor method of assay in the chicken was a more reliable evaluation of the oxytocic principle than the former assay on isolated uterine strips. Except in cases of separation of the oxytocic and pressor principles, assays of extracts of the posterior lobe of the pituitary are generally carried out by methods dependent upon the activity of the oxytocic hormone.

The powerful contracting action on the uterus of the virgin guinea pig elicited by the oxytocic principle is shown in the tracing of Stewart (1949), figure 46-4. Note the quantitative response of the tissue to increasing quantities of the preparation.

Like the action of ergonovine on the uterus, the action of oxytocin is inhibited by progesterone and intensified by the estrogens. The interrelationship of the various hormones on uterine contraction is shown in the behavior of the cat's uterus to oxytocin. If the nonpregnant uterus of the cat is treated first with oxytocin, epinephrine will cause the uterus to contract instead of relaxing as usual.

The human uterus is most sensitive to oxytocin at the termination of pregnancy. The contracting effect of the drug is not mediated through the autonomic innervation of the uterus. The action is directly on the myometrium. The effect is manifested more strongly on the fundus of the uterus than on the cervix. The pressure in patients 8 to 9 months pregnant was measured by means of an intrauterine balloon. The increased pressure produced by the oxytocic drugs was measured. It was observed that ergonovine and oxytocin can increase the force of uterine contractions to an intensity equal to or greater than that normally present during the delivery of the head. It is suggested, however, that the danger of uterine rupture may be greater when the pressure is induced by drug action, because the prolonged maximal contractions and stress are *"forced on the organ irrespective of its condition."* The stress placed on the wall of the uterus is about 700 gm. /sq. cm. of cross-section area.

Caldeyro-Barcia *et al.* (1957) studied the effect of a continuous infusion of synthetic oxytocin on uterine contractility in pregnant women. They

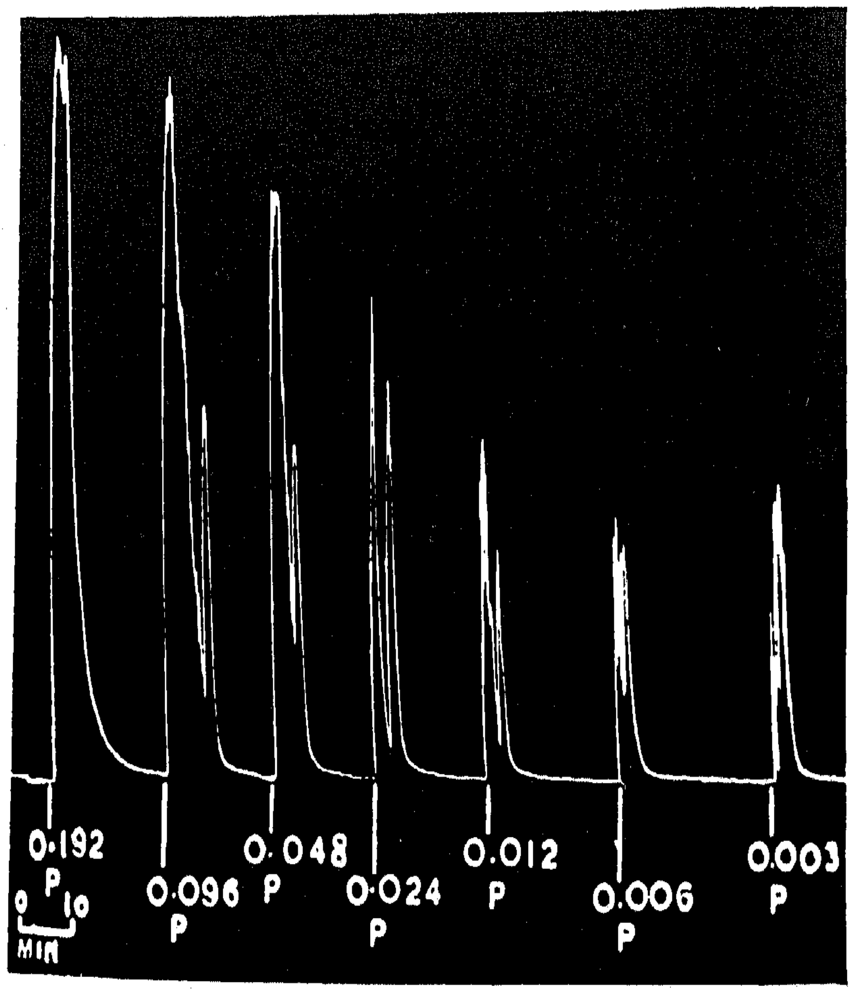


FIG. 46-4. The response of the isolated uterus of the guinea pig to Pitocin (oxytocin). Uterus is treated first with stilbestrol. *P*, dose of Pitocin in milliunits. (From G. A. Stewart, J. Pharm. & Pharmacol., 1: 436, 1949.)

measured amniotic fluid pressure to give an isometric tracing of uterine contractions. Uterine activity was calculated as the product of the intensity multiplied by the frequency of contractions. Oxytocin infusion evoked an increase of the intensity and of the frequency of contractions. They observed an exponential relationship between the infusion rate of oxytocin and the increase in uterine activity. Their studies indicated that in normal pregnant women at term the infusion rates between 1 and 8 mU./min. increased uterine activity to values similar to those recorded at the end of the first stage of normal spontaneous labor. Based on the assumption that the secretion of endogenous oxytocin is the prime factor in producing uterine activity during the first stage of labor, they conclude that the endogenous secretion rate of the hormone is between 1 and 8 mU./min. It is of special interest to see this attempt to place the administration of oxytocin on a quantitative physiologic basis.

Evidence is accumulating from various sources to indicate that endogenous oxytocin plays an important role in parturition. The electrical stimulation of the neurohypophysis of the rabbit results in the secretion of oxytocin and significantly increases uterine activity at parturition. Fitzpatrick (1960) found significant rises in blood-oxytocic levels in ewes during labor and delivery. In pregnant women oxytocin is the only known agent which, when administered, is capable of producing uterine contractions indistinguishable from those of normal labor.

There is further evidence to indicate that oxytocin activity is terminated by an enzyme known as *oxytocinase*. The enzyme is present in the plasma of pregnant women and appears to originate in the pregnant myometrium and placenta. The activity of oxytocinase is low at the onset of pregnancy and is maximal at the time of labor. It appears possible that the anti-oxytocin activity of the plasma of pregnant women may be dependent upon nonspecific aminopeptidases, as suggested by Tuppy and Nesvadba (1957). It is established, however, that endogenous oxytocin plays an important role in human parturition and that the termination of its activity is mediated through enzymic activity.

**Other actions of oxytocin.** Oxytocin produces a slight increase in oxygen consumption in man. Its effects on the circulation are negligible (Grollman and Geiling, 1932). Gaddum (1928) stated that oxytocin caused a transient fall in blood pressure in some cats. Stehle (1933), from studies on dogs, believes pressor and depressor actions may be inherent properties of the oxytocic molecule. Melville (1936) observed that oxytocin antagonized but did not abolish the cardiac effects of vasopressin.

Woodbury and associates (1944) observed great species variation in the cardiac response to oxytocin. In man, oxytocin transiently reduces the blood pressure, weakens the cardiac contraction, and usually influences the electrocardiogram. Vasodilatation is sometimes produced by oxytocin, but it is independent of, and is not the cause of, the cardiac and the immediate blood pressure changes.

It was observed that extracts of the posterior lobe of the pituitary produced glycosuria in rabbits. When Kamm separated the 2 principles, it became interesting to determine which of the 2 substances evoked the hyperglycemia. It was observed that both vasopressin and oxytocin were capable of elevating the blood sugar level of the rabbit. The hyperglycemia evoked by oxytocin is not as intense but is more prolonged than that produced by vasopressin. These investigators observed that treatment with alkali at normal temperature destroyed the hyperglycemic action of vasopressin. This treatment only partially reduced the hyperglycemic activity of oxytocin.

Larson (1939) demonstrated that when an extract of 3 to 8 mg./kg. of pituitary powder is injected intravenously into anesthetized cats or dogs, 30 per cent of the oxytocic principle is excreted in the urine within 2 hours. Larson showed also that the oxytocic principle can be inactivated by polypeptidases present in tissues.

One of the specific actions of oxytocin is that of inducing milk ejection. Oxytocin stimulates the contraction of the mammary gland musculature, forcing the milk from the alveoli into the ducts. The action of oxytocin causes milk flow but does not increase the quantity of milk. Nickerson (1954) found this response elicited by 0.2 ml. of oxytocin intramuscularly and by 0.05 ml. intravenously. It appears that suckling evokes the release of oxytocin from the pituitary gland. This action is blocked by epinephrine or fright. After suckling, however, the injection of oxytocin will cause a further increase in milk release. Because of this action oxytocin has been used with success in mammary engorgement.

**Oxytocin and synthetic oxytocin (Syntocinon).** Synthetic oxytocin is being widely accepted as a substitute for oxytocin. Lipton *et al.* (1962) critically studied the 2 agents when administered intravenously to anesthetized and unanesthetized subjects. They concluded that each agent is compatible with the anesthetics commonly used in obstetrics. When administered intravenously to anesthetized or unanesthetized subjects, oxytocin and Syntocinon produced no cardiovascular effects when the solutions were well diluted. In concentrated doses each evoked hypotension and electrocardiographic changes. The EKG changes were more marked with oxytocin than with Syntocinon. They showed that oxytocin elicited an epinephrine-potentiating effect on the rat's mesoappendix which was not produced by Syntocinon. Oxytocin contains, as a rule, 2 contaminants, vasopressin and animal protein. The presence of stress may play a role in the production of cardiac arrhythmias during the administration of oxytocin (with its naturally-occurring contaminants), especially when the heart is sensitized by an anesthetic. From the evidence available, it appears that of the 2 agents synthetic oxytocin (Syntocinon) is the drug of choice.

Syntocinon may be effectively administered internasally. Hendricks and Pose (1961) used the drug in a nasal spray to combat uterine inertia. The solution, containing 40 units/ml., is administered from a 5-ml. plastic "squeeze bottle" to both nostrils. The uterine effect occurs in 5 to 15 minutes and slowly subsides. These investigators are of the opinion that the method is especially safe. Also the method holds promise as an oxytocin sensitivity test.

**Therapeutic use of oxytocin.** The principal use of oxytocin is to *check postpartum bleeding after the baby is born*. For this purpose 0.3 to 1 ml. (3 to 10 units) intramuscularly, given at the time the baby's anterior shoulder is being delivered, will usually hasten the separation of the placenta. It is possible, however, for the action to be prompt enough to cause the cervix to clamp down before the placenta is delivered.

Another method of using oxytocin is by an intravenous drip. The drug is added to saline, glucose, or whole blood, and the rate of flow is regulated so that the patient receives any predetermined dosage. Prior to the delivery the recommended dose is 0.02 to 0.03 ml. each ½ hour. After the completion of the third stage this may be increased to as much as 1 ml./hour. The advantages for this method are as follows:

1. The uterus is subjected to a constant mild stimulation rather than to a series of much stronger effects. The action can be prolonged for as great a period as desired.
2. The uteri of different patients react differently to the same dose of oxytocin. In one instance the response may be very slight, in another extremely vigorous, so that there is real danger of rupture of the organ or of a tetanic contraction so strong and so long in duration as to cause asphyxia of the baby. If the drug is being given by intravenous drip, the dose is never large at any one time, and if an untoward reaction occurs the drug can be discontinued.

Oxytocin is useful to check bleeding in cases of septic abortion. The dose is 0.5 ml. (5 units) intramuscularly, 4 to 6 times daily.

Oxytocin may be used to induce labor by slow intravenous infusion. Stone and Gordon (1954) used 0.5 ml. of oxytocin in 500 ml. of 5 per cent dextrose injection. This procedure of using a diluted oxytocin solution is in accordance with the principles previously mentioned. Clyman *et al.* (1959) made a survey of births in New York City with regard to infant mortality, socio-economic status, and the use of oxytocics. Their data showed that in breech deliveries and cesarean sections the use of oxytocin to induce labor markedly increased infant mortality.

Oxytocin is used infrequently to control breast engorgement. This elicits the "let-down" reflex causing milk to flow toward and through the nipple. This is advantageous where the sucking activity of the baby is too weak to effect the "let-down," or where the sucking is unusually long and hard and might traumatize the nipples.

### Sparteine Sulfate

**Sparteine Sulfate (Tocosanine).** Sparteine is an alkaloid obtained from *Sarothammus scoparius* (broomtop). Its sulfate is a white, crystalline powder, readily soluble in water. For many years the alkaloid was used as an antiarrhythmic agent similar to quinidine. Kreitmair (1936) observed that the drug evoked a strong oxytocic action when administered intravenously to a pregnant cat. Caldeyro-Barcia and Alvarez (1952) demonstrated that 150 mg. of sparteine sulfate evoked a short period of uterine hypertonus, followed by an increase in the intensity of contractions and speed of dilatation in pregnant women. This response was confirmed by several investigators and initiated a revival of interest in sparteine.

In America the use of sparteine in obstetrics was pioneered by Plentl *et al.* (1961). They used the drug in more than 1500 cases and concluded that it was an effective oxytocic for the treatment of primary and secondary uterine inertia and for all forms of desultory labor. Burke *et al.* (1962) found sparteine successful in 86.7 per cent of 150 cases. They felt that it had no special advantage over other oxytocics as far as efficacy was concerned. However, they commented favorably on the ease of administration, absence of uterine rupture or tetanic contractions in all cases, and the lack of maternal or fetal morbidity. It does appear that the advantages of sparteine stem from the rapid induction of uterine contractions evoked by a single intramuscular dose and the freedom from side effects and overdosage. For example, Plentl used 1650 mg. in multiple doses of 150 mg. each without observable untoward effects. No significant changes in blood pressure have been observed following the administration of sparteine.

Sparteine is contraindicated in cardiac patients and in those exhibiting normal and forceful labor. Also it is not recommended in obstetrical complications in which other oxytocics are contraindicated.

The drug is available in a solution of 0.45 per cent saline, containing 150 mg. of sparteine sulfate in 1 ml. The initial dose is 1 ml. given intramuscularly only. This dose may be followed by successive doses of 1 ml. in 1½ to 2 hours until 4 doses have been given. This drug has strong and well established competition in ergonovine and oxytocin; it will be interesting to observe whether or not it will take a leading place in modern obstetrical practice.

### Nonsteroidal Ovarian Hormones

The ovary elaborates nonsteroidal principles which elicit a relaxant action upon the uterus. The investigations of Hisaw *et al.* (1929 *et seq.*) clearly demonstrated that such a principle or principles could be extracted from the ovary. He designated the substance as "relaxin." Preparations of this character have been found useful in the treatment of *repealed abortion* and in *dysmenorrhea*. Frieden (1959) employed counter current distribution technics to demonstrate that ovarian extracts contain a *uterine-relaxing factor* and a *cervical softening factor*. There are 2 products available in therapy which contain varying proportions of these ovarian factors. One of these is *Lututrin* (*Lutrexin*) and the other is *Releasin*.

**Lututrin (Lutrexin).** The use of Lutrexin in dysmenorrhea is discussed on page 788. Majewski and Jennings (1955) used Lutrexin satisfactorily in the treatment of premature labor. They observed a definite decrease in premature births in a series of over 1600 cases in which Lutrexin was administered. The dosage of Lutrexin administered was 4000 units initially, followed in 1 hour by 3000 units and by 1000 units hourly thereafter until contractions ceased clinically and symptomatically. Lutrexin is administered orally without untoward side effects. They state: "The results show one method of treatment that may lead to the salvage of a number of infants."

Rezek (1959) confirmed the value of Lutrexin in premature labor in a series of 54 cases. He was able to check 40 cases (74 per cent) for at least 28 days. He is of the opinion that many infants were salvaged by the treatment who would have otherwise died because of prematurity. It appears that although the uterine-relaxing factor of the ovary has not been isolated as a chemical entity, it is present in Lutrexin in therapeutically demonstrable quantities.

Each tablet of Lutrexin contains 2000 units.

**Releasin.** This product of ovarian extraction is a purified preparation of "relaxin" (Hisaw), the hormone of pregnancy responsible for pubic relaxation or separation of the symphysis pubis in mammals. The hormone appears in the blood of women during gestation and disappears within 24 hours after delivery. Evidence suggests that relaxin is not a single chemical entity. Frieden *et al.* (1960) subjected a relaxin preparation to counter current distribution and observed that biologic activity was distributed over a wider band than was expected from a single component. By refractionation of the active band, 3 peptides with relaxin activity were isolated.

Steinetz (1963) obtained a fraction of high biologic potency (1800 units per mg.) that showed some electrophoretic heterogeneity. The molecular weight appeared to be between 8,000 and 10,000. The amino acid constitution of the principle was determined. Rudzik and Miller (1962) showed that the uterine inhibitory activity of relaxin is mediated indirectly through the release of catecholamines, of which epinephrine appeared to be the most important. The administration of relaxin produced a reduction in the epinephrine content of the uterus.

Releasin is used in the treatment of premature labor. If administered soon enough, it may check premature labor. Often it provides additional time for the fetus *in utero* to permit the delivery of a viable fetus. Folsome *et al.* (1956), in a large series of cases of premature labor treated with Releasin, claimed to decrease the "fetal wastage" by 61 per cent. Holmstrom (1958) found Releasin valuable in checking premature labor in 50 to 55 per cent of his patients; rest and sedation were effective in 30 to 35 per cent of the cases. He states: "There is slight evidence to indicate that Releasin is effective in postponing the onset of true labor, in some cases."

Releasin in premature labor is administered intramuscularly in an initial dose of 2 ml., with 1 ml. every 2 hours until labor is arrested. If no response is elicited by 3 or 4 injections, the drug is not likely to be effective. Releasin may also be given by intravenous drip, 2 to 5 ml. in 500 ml. of normal salt solution over a 4-hour period.

Releasin has been used in the treatment of scleroderma with some degree of success (Casten and Boucek, 1958). There is also some evidence that this agent might be of some value in the treatment of occlusive peripheral vascular disease.

Although definitive progress has been made, this whole problem urgently awaits clarification and simplification, which can be achieved only by the isolation and chemical characterization of the pure hormonal substance or substances from the ovary. The lack of this information, the oral administration of one substance presumably polypeptide in nature, and the parenteral administration of another befogs the issue of their definitive therapeutic value.

### Drugs and the Placental Barrier

Since the thalidomide tragedy there has been an awakening of interest in the passage of drugs through the placental barrier and their subsequent effect upon the fetus. Perhaps the most important cause of the toxicity of drugs to the fetus is the fact that the enzyme systems required for their detoxification are not available or not yet fully developed. For example, the livers of newborn animals are deficient in enzymes necessary to synthesize and conjugate glucuronide, a pathway through which many drugs are detoxicated.

In general, evidence indicates that drugs of small molecular weight are transported through the placenta more readily than those of higher molecular weight (Hagerman and Villee, 1960). Most drugs that have a molecular weight of less than 1000 (and this includes most of the commonly used drugs) will cross the placental barrier. The subject of placental transport of drugs was reviewed by Friend (1963), and a summary of his work embracing the major classes of drugs is given.

Analgesics, sedatives, and tranquilizers affect the central nervous system of the fetus. The most commonly used narcotic analgesics are morphine and meperidine. Morphine readily crosses the placenta, and the typical effects on the newborn include myosis, cyanosis, severe respiratory depression, and withdrawal symptoms. Nalorphine crosses the placenta and if given to the mother just prior to delivery or to the newborn, corrects and prevents the effects of morphine. Nalorphine alone can also cause a withdrawal syndrome in infants.

Among the commonly used non-narcotic analgesics are aspirin and phenacetin. Aspirin crosses the placenta and has been measured in umbilical cord blood. Aspirin has caused abortions but there are no known damaging effects on the fetus. Phenacetin can cause anemia, methemoglobinemia and sulfhemoglobinemia. When phenacetin has been taken for prolonged periods of time, serious renal damage to the mother and to the offspring have been described. Hyoscine, paraldehyde, chloral hydrate, and ethyl alcohol all cross the placenta. There are known harmful effects upon the fetus from hyoscine and ethyl alcohol. Paraldehyde given to the mother can result in a drowsy newborn, but no respiratory depression has been described. Even though there are no reports of toxicity to newborns or prematures attributed to the chloral hydrate given to the mother, the drug must be detoxified by hepatic glucuronic acid conjugation, so that it seems best to avoid its use in premature deliveries.

The barbiturates cross the placenta and can depress the newborn for several days, but no known permanent damage to the fetus has been described. Of the various stimulants used, norepinephrine and epinephrine cross the placenta but cause no known harmful effects on the fetus. Norepinephrine does not cross the blood-brain barrier of the adult. Tranquilizers such as reserpine and the phenothiazines have not been proved to be toxic to the fetus.

Drugs taken during pregnancy affect many other organ systems. Digitoxin passes the placenta and probably can be metabolized by the human fetus, but no known harm to the fetus has occurred with therapeutic doses. The injection of pressor amines into the mother causes asphyxial effects in the fetus, although the fetus is apparently less sensitive to their effects than the mother. If ganglionic-blocking agents are used in pregnant women, they should be used with caution since they cross the placenta and in the sheep fetus may cause a fall in blood pressure, cardiac slowing, and some fetal hypoxia. There is no evidence that heparin crosses the placenta or harms the fetus, but the harmful effects of Dicumarol on animal fetuses indicate that this drug is probably dangerous to the human fetus. The risk to the fetus of quinine ingestion by the pregnant woman has probably been overemphasized in the past. Congenital defects are neither more frequent nor more extensive in these infants and there is probably no increased incidence of fetal deafness from the use of quinine during pregnancy.

Cases of jaundice and possibly death have been attributed to the use of sulfonamides during pregnancy. No known damage has occurred to the fetus from the use in pregnant women of penicillin, erythromycin, vancomycin and isoniazid, but eighth nerve damage from streptomycin and jaundice from chloramphenicol administration to the newborn have been reported. No case of chloramphenicol toxicity in the newborn following its use in the pregnant woman has been described, although this possibility should be considered.

Certain cytotoxic agents have been shown to be harmful to the human fetus; aminopterin has a selective toxicity for the fetus. The corticosteroid hormones have no known harmful effect on the human fetus. Radioiodine readily causes fetal damage, including involution of the fetal thyroid, colloid goiter, and chromophobe adenomas of the pituitary in animals. Propylthiouracil and methimazole may produce goiters in the fetus. Succinylcholine, used extensively as a muscle relaxant in obstetrics, apparently does not harm the fetus. There are some data suggesting that nicotine, lead and other heavy metals may be harmful to the fetus.

It is clear from the review that the placenta permits the passage of most drugs to the fetus, and during the period of gestation great caution must be exercised in the administration of drugs. The Commission on Drug Safety very cogently commented in this regard, "Animal tests available at the present time do not guarantee drug safety to the unborn child."

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# 47

# *The Pharmacologic Response of the Reproductive System to the Gonadotropins*

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According to an Egyptian papyrus, approximately 4000 years old, women who wished to know whether or not they were pregnant were given the following suggestion. Plant some barley seeds in a small vessel containing earth and add a small quantity of urine each day. If the barley grows, the pregnancy test is positive. If it fails to grow, the test is considered negative (Aschheim, 1935). It has been established that the urine of nonpregnant women contains very small quantities of *estrogens.* Early in pregnancy the quantity increases greatly, and estrogens are stimulants to plant growth. The pregnancy tests of Aschheim and Zondek and other investigators are dependent upon the determination of gonadotropins in the urine by injection into animals such as the frog, rabbit, and rat. Estrogens are present in increased quantities in the urine in the early part of the menstrual cycle. The initiation of the menstrual cycle, however, occurs in the *anterior lobe of the pituitary gland.*

## Hormones of the Anterior Pituitary Gland

The hormones of the anterior pituitary gland concerned with reproduction are: (1) follicle-stimulating hormone, FSH; (2) interstitial cell-stimulating hormone, ICSH; and (3) luteotrophic hormone, LTH.

These substances are protein in nature and are apparently secreted from the anterior pituitary gland. Prior to the onset of menstrual flow, the human female begins a secretion of FSH. This substance may be demonstrated in the urine. In addition, its presence is announced through its effect on ovarian function. The early sexual maturation processes are dependent upon the ovarian secretion of estrogens. Ovarian secretion of estrogens is dependent upon the presence of circulating FSH. The early maturation processes, consisting of breast development, somatic growth, bone development, and the presence of sexual hair, are estrogen-dependent phenomena that occur prior to the menarche.

With the advent of menstrual flow that is usually anovulatory and dependent upon an excess of circulating estrogen, total maturation of the ovary is accomplished through the action of the remaining 2 gonadotrophic substances.

It is currently believed that the ovary, prior to the time of ovulating, secretes the steroid hormone progesterone. Circulating progesterone activity causes the anterior pituitary gland to secrete ICSH. ICSH, in turn, activates the ovulation mechanism of the ovary which has previously been prepared for this activation through follicle development by the influence of FSH.

The transformation of the Graafian follicle from an unruptured cyst to a ruptured follicular cyst in which there is proliferation of the granulosa cells is apparently the result of ICSH and the third gonadotrophic hormone, LTH. It is presumed that LTH provides the stimulus through the corpus luteum of the ovary for a continued viability and secretion of progesterone through the 14 days characteristic of the luteal phase of the menstrual cycle.

At this point in the reproductive cycle, menstruation occurs in the absence of pregnancy. Menstruation in the ovulatory cycle is dependent upon the withdrawal of the steroidal hormones, estrogens, and progestins in the support of the secretory endometrium. This results in the constriction of the spiral arterioles of the endometrium and necrobiosis of the endometrium in its subsequent slough.

Should pregnancy intervene, the menstrual mechanism is thwarted by the appearance of a fourth gonadotropic substance. This gonadotropin in the human is commonly referred to as human chorionic gonadotropin (HCG). It is secreted by the Langerhans' cells of the chorion. HCG has been shown to be luteotropic. It appears that the luteotropic activity of the chorionic gonadotropin provides the stimulus for the prolongation of the life of the corpus luteum. Owing to the continued function of this structure, it is designated as the corpus luteum of pregnancy. The corpus luteum of pregnancy and the ovary provide the estrogen and progestational hormones required for the maintenance of pregnancy until approximately 60 days of gestation, at which time the placental tissue secretes estrogen and progestational agents in sufficient amounts to support the pregnancy even in the absence of ovarian function.

Therefore, ovarian function is considered to be 2-fold. The first phase is the secretion of estrogen. The second phase is the ovulation mechanism followed by the secretion of progesterone. During the maturation process, the ovary of the human female secretes only estrogen. The total maturation of the pituitary ovarian axis results in the pituitary stimulation of the ovary to the second phase of function, followed by ovulation and corpus luteum formation. At the termination of the reproductive cycle, ovarian function does not cease immediately, but undergoes a serial regression similar to that occurring prior to the menarche. The second phase of ovarian function, ovulation and corpus luteum formation, is lost. The ovulatory cycles are replaced by anovulatory cycles that provide a single stimulus to menstrual flow, that is, the secretion of estrogen. The anovulatory cycle is characteristically irregular and unpredictable in duration, frequency, and amount of flow.

### Anterior Pituitary and Chorionic Gonadotropins

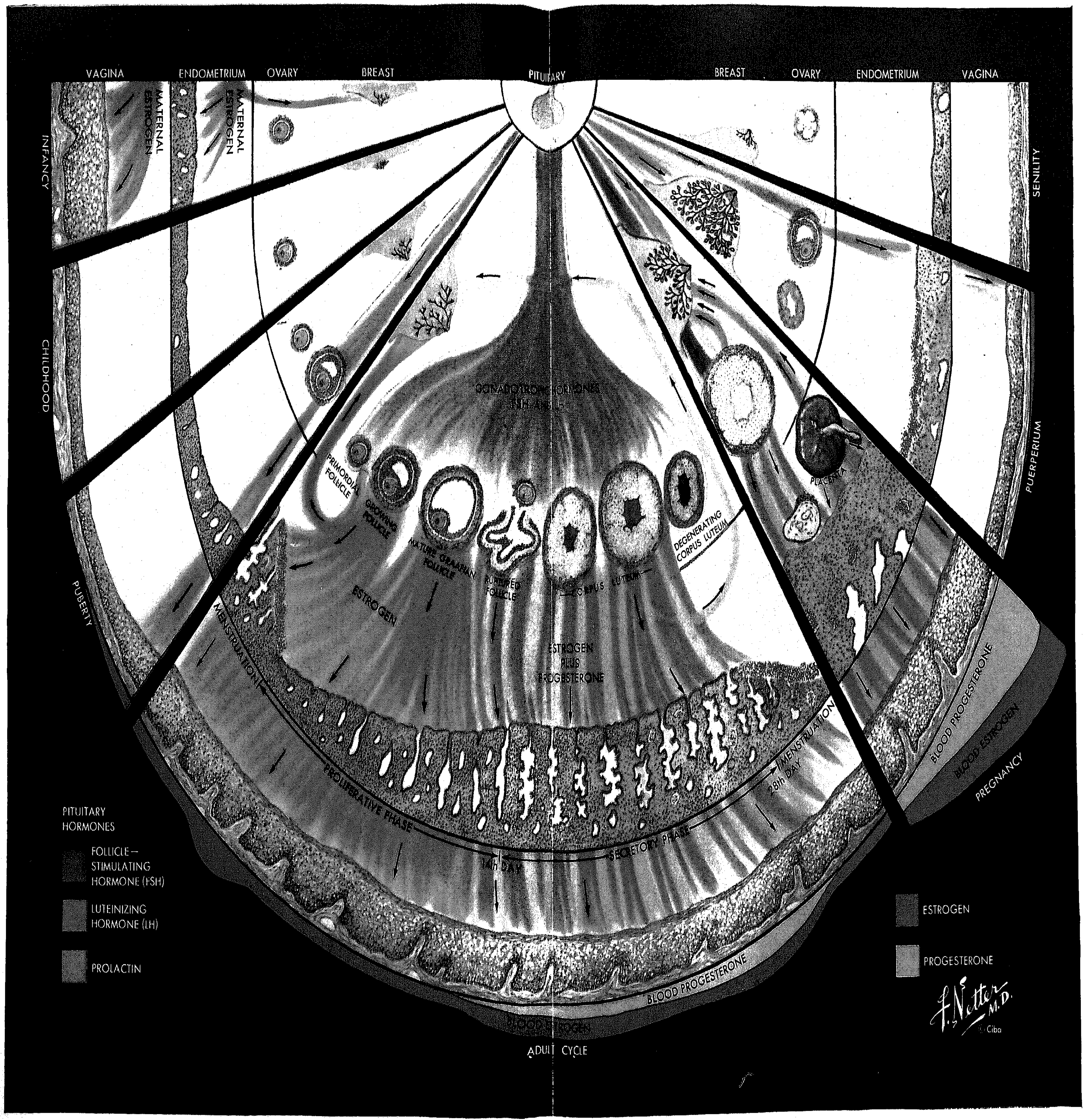
**Follicle-stimulating hormone.** FSH has been isolated from the anterior pituitary of sheep, swine, and humans. Chemically it is a glycoprotein with a molecular weight that varies with the source of the material. FSH has not been crystallized. It is rarely obtained uncontaminated with other pituitary hormones. The urine of human castrates is an excellent source of the hormone. The absence of the gonadal hormone abolishes its restraint on the secretion of FSH by the pituitary gland.

FSH from animals other than human has been used successfully in the stimulation of the human ovary to secrete estrogen when the absence of gonadotropic activity of the pituitary has been established. In the presence of normal ovarian pituitary relationships, the administration of FSH will occasionally cause polycystic enlargement of the human ovary, as well as those of other mammals.

The use of bovine or porcine FSH in humans results in the formation of an antihormone response. This presumably is due to foreign protein rather than to the gonadotropin. Antihormone formation will often result in lessened secretion of endogenous FSH following the administration of the exogenous hormone.

The most satisfactory bioassay method for FSH apparently is the administration of the test substance to immature rats or mice. If FSH is present, the immature ovary is stimulated to the secretion of estrogen. Examination of the uterus of the test animal at a suitable period of time (usually 3 or 4 days) after the initial administration of the test dose will show evidence of increase in uterine weight owing to

Plate 1. Normal menstrual cycle showing pituitary, ovarian, and endometrial activity. (From *CIBA Collection of Medical Illustrations*, Volume 2, Section 6, "Reproductive System.")


VAGINA
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CHILDHOOD
PUBERTY
SENILITY
PUERPERIUM
PREGNANCY
GONADOTROPIC HORMONES
FSH AND LH
PRIMORDIAL FOLLICLE
GROWING FOLLICLE
MATURE GRAAFIAN FOLLICLE
RUPTURED FOLLICLE
CORPUS LUTEUM
DEGENERATING CORPUS LUTEUM
PLACENTA
ESTROGEN
ESTROGEN PLUS PROGESTERONE
MENSTRUATION
PROLIFERATIVE PHASE
14th DAY
SECRETORY PHASE
MENSTRUATION
28th DAY
BLOOD PROGESTERONE
BLOOD ESTROGEN
BLOOD PROGESTERONE
BLOOD ESTROGEN
ADULT CYCLE
PITUITARY HORMONES
FOLLICLE-STIMULATING HORMONE (FSH)
LUTEINIZING HORMONE (LH)
PROLACTIN
ESTROGEN
PROGESTERONE
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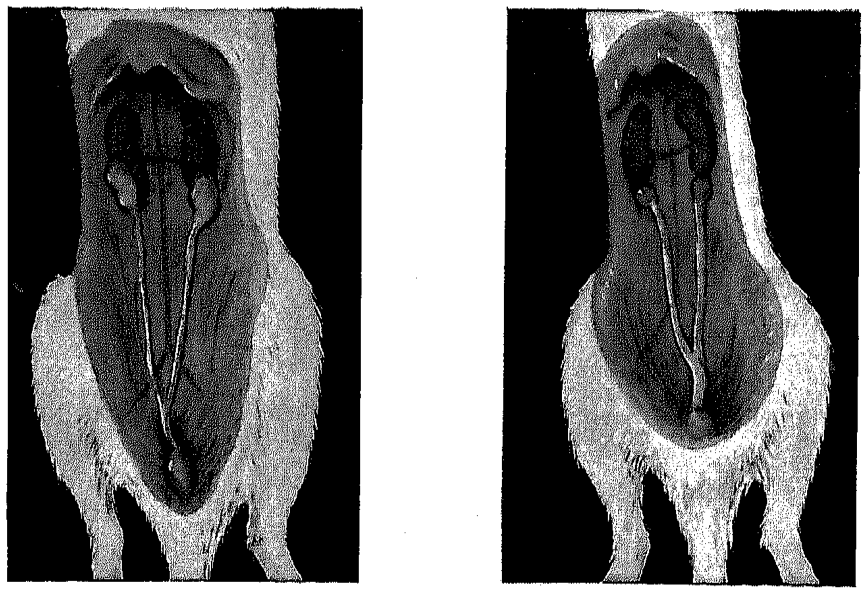
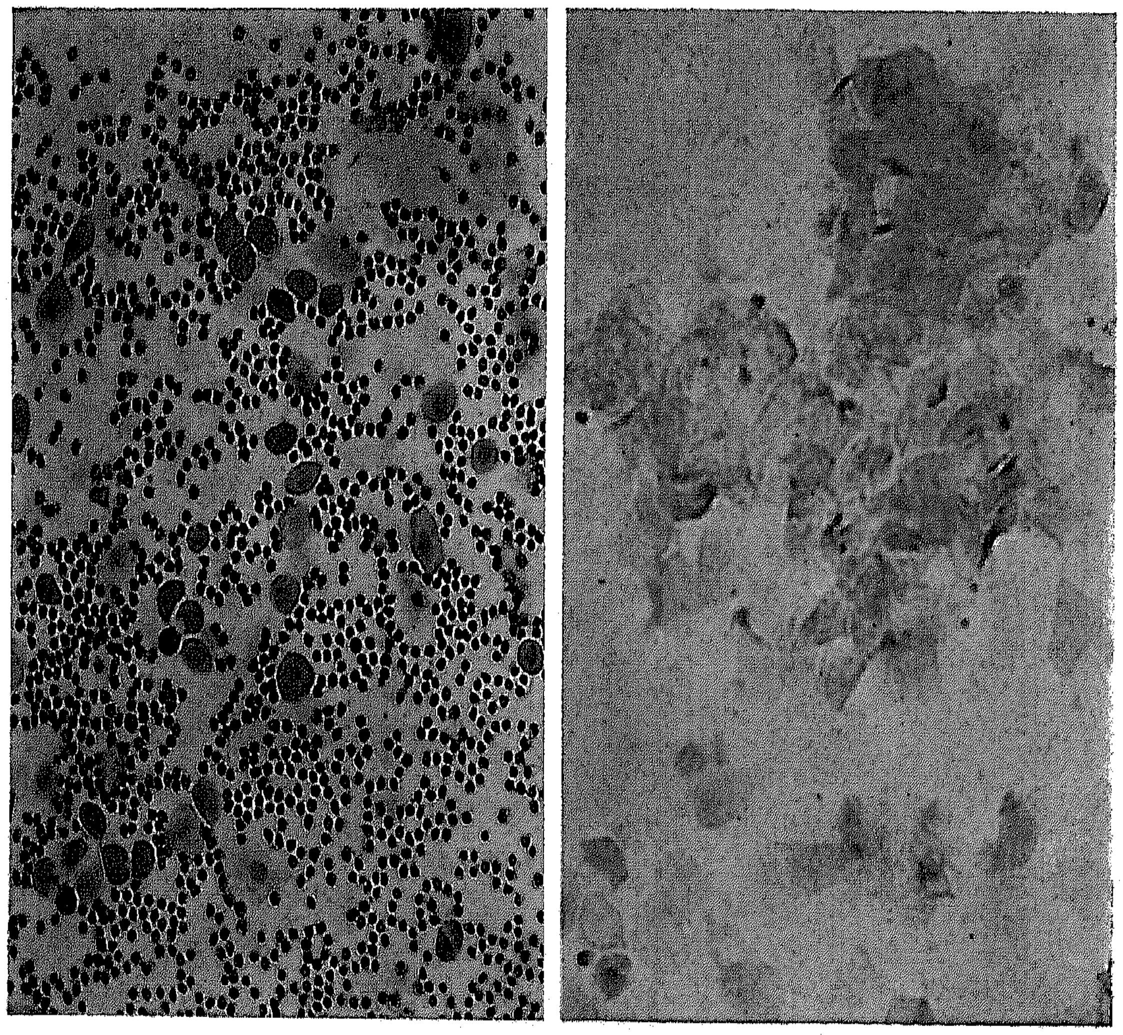


Ovaries of Immature Rat Normal

Ovaries of Rat After Injection of Gonadotropins

Plate 2



A

B

Plate 3. Vaginal smears of rat. *A*, diestrus—the resting stage found in the ovariectomized rat. The smear shows leukocytes and epithelial cells. *B*, estrus—the heat period induced in the ovariectomized rat by the injection of estrone. The smear shows large, cornified cells which are non-nucleated.

the presence of circulating estrogen. This test is sensitive despite the fact that the FSH is utilized in this indirect method.

**Interstitial cell-stimulating hormone.** The interstitial cell-stimulating hormone is also named luteinizing hormone (LH). The terminology *interstitial cell* is preferred to *luteinizing* because of the similarity of luteinizing hormone to luteotrophic hormone. This substance, apparently secreted in its greatest amount at the midportion of the cycle about the time of ovulation in humans, is considered to be a glycoprotein. It has not been crystallized and the molecular weight has not been determined.

The optimal activity of ICSH seems to be dependent upon the presence of FSH. Unusually high levels of ICSH, as described in the Stein-Leventhal syndrome, fail to induce ovulation.

Since ICSH is not available in sufficient quantity to be used clinically, no reliable observations have been made regarding its activity in patients.

**Luteotrophic hormone.** This substance is also called *lactogenic hormone* and *prolactin.* It is apparently responsible for the continuation of the life of the corpus luteum of a normal menstrual cycle for its normal span of 14 days. The cyclic and almost constant duration of the corpus luteum is well known. The manner in which this cycle or constant duration of function is attained is not known. LTH has been characterized as a protein, water-soluble hormone which contains no carbohydrate. LTH presumably appears during the postovulatory phase of the menstrual cycle and continues to be secreted until prior to menstrual flow. Should pregnancy intervene, LTH is most evident approximately 3 or 4 days following parturition. At this point, engorgement of the breasts and milk secretion indicates the presence of LTH. The absence of LTH until the maternal blood is cleared of estrogen and progestational agents suggests that these substances have a repressive effect on the lactogenic hormone. There is, however, no direct evidence indicating that LTH can be suppressed by the administration of estrogen, androgens, or progestational substances after parturition.

Like ICSH, LTH exists in quantities not available for research on human beings.

**Chorionic gonadotropin (HCG).** Gonadotropic substances in the urine of pregnant women were first described by Aschheim and Zondek (1928). Human chorionic gonadotropin is considered to be a single substance with the chemical nature of a glycoprotein. This substance is the basis for the majority of pregnancy tests.

HCG is secreted in increasingly large amounts by the placenta until approximately 70 days of gestation (after the last menstrual period). The peak secretion of HCG indicated by serum levels and total urinary excretion is about 500 I.U./ml. of serum. The total amount secreted in the urine at a similar period of gestation is approximately 100,000 I.U. of HCG per L. The major physiologic effect of HCG in human pregnancy appears to be in the luteotropic activity of the substance. Descriptions of the prolongation of the functional life of the corpus luteum in the nonpregnant female by injections of HCG may be found in the work of Browne and Venning (1938) and Brown and Bradbury (1947). These studies indicate that the established corpus luteum may be stimulated to function beyond its ordinary 14 days through the administration of chorionic gonadotropin.

Injection of chorionic gonadotropin into mature, hypophysectomized animals induces thecal luteinization with estrogen secretion. Persistent estrous results; however, maturation of the follicles and formation of corpora lutea do not occur (Selye *et al.*, 1933). If ripe follicles are present at the time of hypophysectomy and chorionic gonadotropin is given immediately, corpora lutea formation may occur.

The gonadal-stimulating action of chorionic gonadotropin exerts an effect upon the testes. It acts upon the interstitial cells, inducing the secretion of androgens. These cause the growth of accessory sex organs. In the monkey chorionic gonadotropin evokes the descent of a testes in the prepuberal animal.

Spermatogenesis is maintained by the gonadotropin in the rat which has been recently hypophysectomized. Spermatogenesis is not produced in normal, immature rats or restored after atrophy by the gonadotropin.

Leach *et al.* (1954) studied the plasma levels of human chorionic gonadotropin in men who received 5000 I.U. of the hormone intramuscularly 3 times weekly. Twenty-four hours after the initial dose, the plasma contained 0.1 to 0.4 I.U./ml. The levels of the hormone remained constant for approximately 4 days. The hormone became undetectable after 7 days. In normal human pregnancy, at the termination of which the normal chorionic gonadotropin level approximates 10 I.U./ml. of serum, the blood is cleared of chorionic gonadotropin in approximately 6 to 12 hours. In general, approximately 10 per cent of exogenous chorionic gonadotropin administered to the human may be recovered in the urine as physiologically active chorionic gonadotropin.

Chorionic gonadotropin (HCG) is prepared from human pregnancy urine in the form of a powder. It is a glycoprotein which contains about 12 per cent of galactose and 5 per cent of hexosamine. The isoelectric point is at pH 3.2. Its molecular weight is approximately 100,000. The powder is assayed by injection into the test animal and compared with the international standard of potency. One I.U. of chorionic gonadotropin is the amount of activity equivalent to that found in 0.1 mg. of the international standard powder of chorionic gonadotropin.

A variety of assay methods are available for determining the presence of HCG. The induction of ovulation in the South African toad (Zenapas pregnancy test) and the spermatokinetic response in the North American male frog are most generally used. The latter test is a rapid, simple, quantitative and qualitative test for the presence of HCG. Spermatokinesis in the *Rana pipiens* occurs within 15 minutes to 2 hours after the administration of chorionic gonadatropin. There is a seasonal variation in response of this frog to chorionic gonadotropin. During a period of average sensitivity, 100 I.U. of HCG will cause a positive response within 30 minutes; 30 I.U. of HCG is required to elicit a positive response in 50 per cent of the animals injected.

HCG is available for intramuscular injection in sterile solutions of different potencies such as 100, 500, and 1000 units/ml. The powder and sterile distilled water are provided in separate containers.

**Therapeutic use of chorionic gonadotropin.** The principal use of chorionic gonadotropin is in the treatment of cryptorchidism. Here it is of value when the descent of the testes is not impeded by anatomic abnormality.

The usual dosage schedule is 200 to 500 units intramuscularly 2 to 3 times a week. Repetitious injections may prove dangerous, and further treatment is not advised after 8 weeks if progressive descent does not occur. Signs of precocious maturity warrant the discontinuance of therapy.

For many years gonadotropin of placental origin was used in the treatment of functional uterine bleeding. There is no current evidence that this gonadotropin has any constant effect in this condition.

Human chorionic gonadotropin theoretically should be useful in the treatment of recurrent abortion when such is due to the failure of corpus luteum function of the early part of pregnancy. There is, however, no information available at the present time that indicates the superiority of the administration of HCG for its luteotropic effect on the corpus luteum over the administration of progesterone.

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# 48

# *The Pharmacologic Response of the Reproductive System to the Estrogens and Progesterone*

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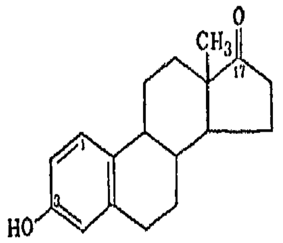
In the preceding chapter consideration was given to the anterior pituitary gonadotropins and the chorionic, pituitary-like gonadotropin. In the schematic representation of the human menstrual cycle (see page 764), it was seen that the initiation of the cycle by FSH induced the ovary to secrete *estrogens* early in the menstrual cycle. Since the ovary is the source of the estrogenic substance, various investigators sought to extract the estrus-inducing substances from the ovary.

## Isolation of Estrogens

Allen and Doisy (1923) observed that an alcoholic extract of the ovaries was capable of producing estrus. Thus an estrus-inducing substance was found to be present in ovaries, follicular fluid, and in large quantities in the mammalian placenta. Another advance was made through the discovery of Aschheim and Zondek (1928) that the estrus-producing hormone was excreted in the urine during mammalian pregnancy.

Groups of investigators throughout the world began to study the chemical properties, and in a relatively short period of time the hormone was obtained in a crystalline form. Doisy *et al.* (1929) in America and Butenandt (1929) in Germany independently, and almost simultaneously, announced the crystallization of the substance.

Estrone is a phenanthrene derivative, as shown by the structures in the accompanying formulas.



Estrone or Theelin
(3-Hydroxyestra-1,3,5(10)-trien-17-one)

Theelin is from the Greek θηλμ (female). It is of interest to note the relationship between the structures of the female sex hormone, the bile acids, cardiac glycosides, carcinogenic hydrocarbons, vitamin D, and the male sex hormone.

### PHYSIOLOGIC FUNCTION OF ESTRONE

As has been stated previously, the anterior lobe pituitary FSH and ICSH (Prolans A and B) are the links between the pituitary gland and the sex organs. They initiate the maturation of the follicle, which is followed by ovulation and the formation of the corpus luteum. Under the stimulus of the pituitary gonadotropins the ovary produces its own internal secretion, *estrone.* This passes from the ovary to the uterus and the vagina and produces the characteristic changes of estrus. Brown *et al.* (1953) observed in animals and in human subjects that estrogens initially stimulate the pituitary to release gonadotropin. The repeated administration of estrogens, however, represses gonadotropin secretion. This phenomenon is often referred to as the "push and pull" principle which regulates the activity of the anterior lobe of the pituitary (Weiner, 1948). Sulman (1958) demonstrated that when estrogenic substances are injected into female rats the pituitary gland selectively absorbed from the circulation large amounts of the estrogen, in contrast to the muscles, uterus, liver, kidney, or brain. Thus it was proposed that the cumulative presence of the peripheral steroid estrogens in the cells of the anterior lobe of the pituitary blocks its endocrine secretion.

Recent work indicates that the primary hormone of the ovary is *estradiol* (see page 770). It is readily converted into *estrone* and *estriol,* which exert their effects upon the uterus and vagina.

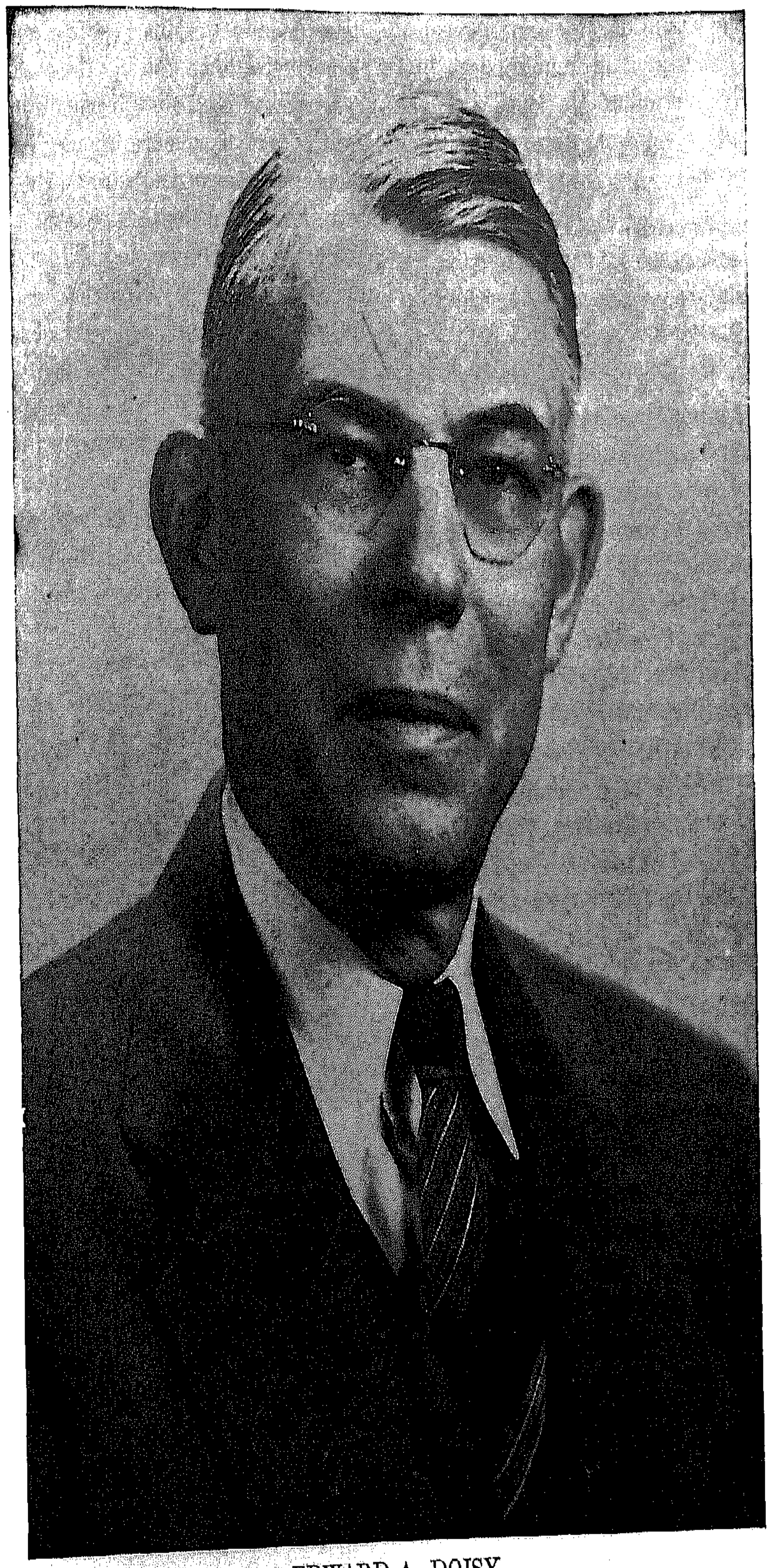
The activity of estrone and other estrogenic substances is measured by their capacity to induce estrus in the mouse or rat. The test is conducted on ovariectomized mice or rats. In the rat or mouse the changes accompanying the reproductive cycle are characterized by a definite cell picture of the vaginal smear. These changes are shown in Plate 3.

**Estrogenic activity at a cellular level.** The effect of estrogens at a cellular level has been studied by numerous investigators. For example, the effects of estradiol on placental metabolism was studied by Villee (1962). He demonstrated that the estrogens increased the rate of turn-over of ATP and increased the rate of production of amino acids by the placental cells. This is suggestive of increased protein, nucleic acid, and fat synthesis induced by the hormone. These findings with placental tissue parallel the results of Mueller *et al.* (1958), who incubated rat uteri *in vitro* sequential to the injection of estradiol *in vivo.* These results appear to support the hypothesis that estrogens in stimulating the pyridine nucleotide transhydrogenase provide an increase in biologically available energy. Evidence of this is demonstrated in an increase of synthesis of proteins, nucleic acids, and fats. These reactions are fundamental to growth. The synthetic estrogens also stimulate the estrogen-dependent transhydrogenase in low concentrations, *e.g.,* $10^{-7}$ M, but evokes inhibition at higher dosage levels (Villee, 1962).

### ASSAY AND STANDARDIZATION

The estrogenic activity of excretions or preparations containing estrogens are expressed in terms of the *International Unit.* This is the amount of estrogenic activity of 0.1 μg. of the standard estrone product stored at the National Institute for Medical Research, London. This international standardization is controlled by a special committee of the World Health Organization of the United Nations. The standard for estrone in the United States is the *U.S.P. Estrone Reference Standard.* The mouse unit, which is the quantity which just suffices to induce estrus in the ovariectomized mouse, varies as tested in different laboratories from 0.04 μg. to 0.1 μg. of pure estrone. The rat unit employed by Doisy is the equivalent of approximately 3 International or mouse units.

The principal value of the biologic method of assay is in the evaluation of the activity of natural sources of estrogens and the determination of estrogenic activity of synthetic compounds. The crystalline estrones are of uniform estrogenic activity.



EDWARD A. DOISY

*Distinguished American biochemist who isolated estrone from urine*

"A crystalline product which has been recrystallized several times has been isolated from urine. The assays show that the crystals are physiologically more active than any preparations obtained thus far, the activity being more than 2000 rat units/mg."

### NATURAL SOURCES OF ESTROGENS

The urine of pregnant women contains about 10,000 mouse units of estrogens per L. This corresponds to about 1 mg. of estrone. Zondek (1930) observed that pregnant mare's urine contains about 10 times as much estrogen as that of pregnant women. Of striking importance was the later observation of Zondek that stallion's urine was richer in estrogens than the urine of pregnant mares. The following data from Zondek (1934) are especially interesting. He found the daily urinary output of estrogens measured in mouse units as follows:

| | |
|---|---|
| 1. Nonpregnant woman | 170 |
| 2. Pregnant woman | 15,000 |
| 3. Nonpregnant mare | 2,000 |
| 4. Pregnant mare | 1,000,000 |
| 5. Stallion | 1,700,000 |

It appears that equines only (horse, zebra, ass) showed a higher estrogen content in the male urine than in the female. Actually it has been shown that the ovaries of the mare contain less estrone than the testes of the stallion.

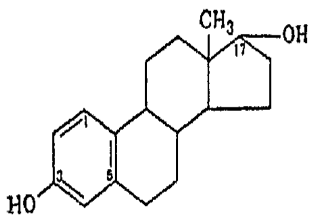
**Character of estrogens in pregnancy urine.** The urine of pregnant women contains at least 3 compounds related to estrone. One of these is *estriol* (theelol), and was isolated by Marrian (1930) and independently by Doisy (1930).

Estriol, although closely related to estrone chemically, having hydroxyl groups at positions 3, 16, and 17, is relatively inactive with regard to estrogen activity. Its activity is approximately $\frac{1}{100}$ that of estrone.

Marrian (1929) isolated another physiologically inactive steroid from pregnancy urine, namely, *pregnanediol*.

Hartmann and Locher (1935) isolated the stereo isomer of pregnanediol, which likewise elicited no estrogenic activity. It is called *allo-pregnanediol*. Pregnanediol is the chief metabolite of *progesterone* (see page 775).

Schwenk and Hildebrandt (1933) reduced the carbonyl group in estrone and obtained the compound with a secondary alcohol group in position 17. It is called *estradiol* or *dihydrotheelin*. The structure is shown in the accompanying formula.

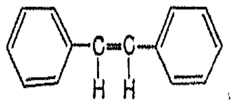


Estradiol-17β
(estra-1,3,5(10)-triene-3,17 β-diol)

This substance is about 10 times more potent than estrone. The activity of the estrogens is dependent upon their method of administration. Sulman (1959) showed that although upon subcutaneous administration in mice estradiol is 10 times more active than estrone and 100 times more active than estriol, these differences in potency vanish upon intravaginal administration. By this route of administration each of the 3 hormones provokes vaginal estrus at the same dosage level. Sulman holds the view that estriol is the vaginal estrogenic hormone and that estrone when injected may be converted into estriol. Estriol was shown to be rapidly metabolized when injected. MacCorquodale *et al.* (1935) succeeded in isolating traces of estradiol from sow's ovaries. One ton of ovaries yielded about 6 mg. of estradiol. Estradiol is present also in the urine of pregnant mares. Pregnant mare's urine contains other steroids with estrogenic activity, namely, *equilin* ($C_{18}H_{20}O_2$) and its isomer *hippulin*. *Equilenin* ($C_{18}H_{18}O_2$) is also present.

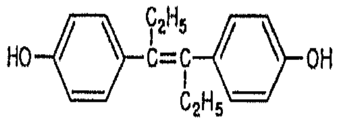
## SYNTHETIC ESTROGENS

It has been demonstrated that the phenanthrene nucleus present in the naturally-occurring estrogens is not essential for inducing estrus. Triphenylethylene $(C_6H_5)_2C{=}CH\cdot C_6H_5$ was observed to exhibit estrogenic activity by Robson and Schönberg (1937). Dodds *et al.* (1938) prepared and studied a large group of *stilbene* derivatives which were found to produce varying degrees of estrogenic activity. The structure of stilbene is shown in the accompanying formula.



Stilbene
Diphenylethylene

The nucleus which gave derivatives high in estrogenic activity was 4,4′ dihydroxystilbene, as shown in the accompanying formula.

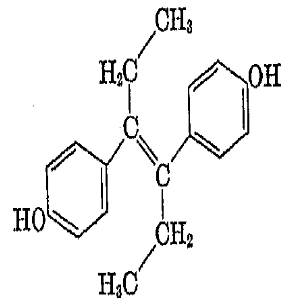


Stilbestrol
(α,α′ diethyl-4,4′-stilbenediol)

**Structure and mechanism of action.** X-ray crystallography has shown that the molecules of diethylstilbestrol and estrone were 8.55 Å long and 3.88 Å wide. Schueler (1946), using these data, postulated that a substance may be estrogenic if its structure is a rather large, rigid, inert molecule with 2 active hydrogen-bonding groups at an optimal separation. Many of the potent estrogenic compounds conform to this molecular description.

Although much information has been accumulated on the activity of the estrogenic hormones, their mechanism of action at a cellular level has not been explained. It seems likely, however, that the synthetic estrogens produce their pharmacologic response through the same mechanism as do the natural estrogens. Each affects certain enzyme systems; however, the alternative possibility of action by participation in specific transfer mechanisms through cytostructural barriers cannot be excluded.

**Diethylstilbestrol, U.S.P.** By replacing the hydrogen atoms of the ethylene residue with alkyl groups from $CH_3$ to $C_4H_9$ and varying the alkyl groups in the same molecule, synthetic estrogens were obtained exhibiting 140 to 3,000,000 mouse units per gm. The compound of choice was the diethyl derivative. It is of interest to write the formula of diethylstilbestrol oriented in space to emulate a natural estrogen, as shown in the accompanying formula.

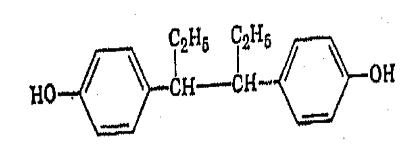


Diethylstilbestrol

*Diethylstilbestrol dipalmitate* is a derivative of diethylstilbestrol. Its action is identical with that of diethylstilbestrol, with the exception of a slower rate of absorption. Hence, its action is more prolonged. It is administered intramuscularly in oil.

Esters of stilbestrol such as the dipropionate are employed also. They are more slowly absorbed and have the advantage of exerting their activity over longer periods of time.

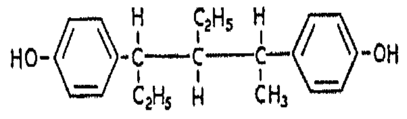
**Other synthetic estrogens.** By the reduction of the double bond in the ethylene residue in diethylstilbestrol, *hexestrol* is formed as shown in the accompanying formula.



Hexestrol, N.F.
(*meso*-3,4-di-parahydroxyphenyl-*n*-hexane)

The action of hexestrol is similar to that of stilbestrol. For menopausal symptoms, 2 to 3 mg. are given daily orally until symptomatic relief is achieved; then 0.2 to 1 mg. is given as a maintenance dose. Hexestrol may also be given intramuscularly, 1 mg. in oil 3 times weekly, with a similar lowering of the dosage for maintenance.

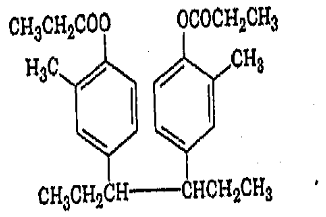
By increasing the length of the alkyl chain separating the 2 phenyl groups in hexestrol, *Benzestrol* is formed as shown in the accompanying formula.



Benzestrol
[3-ethyl-2,4-*bis*(*p*-hydroxyphenyl)hexane]

The action of Benzestrol is similar to that of stilbestrol. For menopausal symptoms, 2 to 3 mg. are given daily orally until symptomatic relief is obtained. Benzestrol may also be given intramuscularly, 2 to 5 mg. in suspension daily for 4 to 7 days.

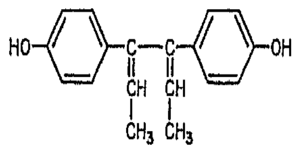
**Promethestrol Dipropionate.** This substance is known under the name of *Meprane dipropionate*. Its action and uses are similar to those of the diethylstilbestrol. It is administered in doses of 1 to 5 mg. daily in tablets. The relationship of this compound to diethylstilbestrol may be observed from the accompanying formula.



Promethestrol Dipropionate
Meprane Dipropionate
[4,4′-(1,2-diethylethylene)di-*o*-cresol dipropionate]

The action of promethestrol dipropionate is similar to that of stilbestrol. In the treatment of menopausal symptoms it is given orally, 1 mg. 3 times daily. When symptoms subside the dose is reduced to 1 mg. daily for maintenance.

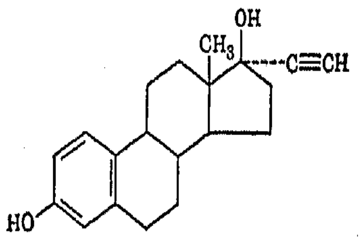
**Dienestrol, U.S.P.** This substance is reputed to be a very active and nontoxic estrogen. The incidence of toxic effects have been said to be less than 1 per cent. It is claimed to be 2 to 10 times as active as diethylstilbestrol. Its structure is shown in the accompanying formula.



Dienestrol, U.S.P.
[3,4-bis(*p*-hydroxyphenyl)-2,4-hexadiene]

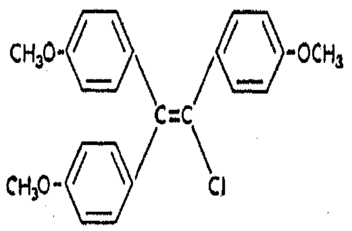
The oral daily dose is 0.1 to 0.5 mg. In artificially-induced climacteric, 0.5 to 1.5 mg. may be given daily. Dienestrol may also be administered subcutaneously or intramuscularly in 2.5- to 5-mg. doses once or twice weekly.

**Ethinyl Estradiol, U.S.P.** The substance most closely related chemically to the natural estrogens is *Ethinyl Estradiol*, which is available under the name of *Estinyl*. The presence of the ethinyl group in the molecule retards the degradation of the compound in the stomach, intestine, and liver. Unlike the naturally-occurring estrogens, it is available orally. Side reactions such as headache, nausea, and vomiting are reduced materially by the administration of the total daily dose at bedtime. The maintenance dose is 0.02 to 0.05 mg. daily. Its structure is shown in the accompanying formula.



Ethinyl Estradiol, U.S.P.
Estinyl

**Chlorotrianisene, N.F. (Tace).** This synthetic estrogen is chemically tri-*p*-anisylchloroethylene, as shown in the accompanying formula.



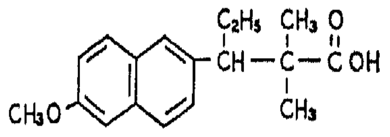
Chlorotrianisene, N.F.
Tace
(chlorotris-*p*-anisylethylene)

This substance occurs as white crystals which are slightly soluble in water.

Chlorotrianisene elicits effects similar to other synthetic estrogens. When it is administered orally, the estrogenic substances excreted in the stools appear to exhibit greater activity than that of the estrogen ingested. This is suggestive evidence that the metabolic changes which occur to chlorotrianisene in the body enhance its activity. Incubation with liver homogenates also increases the activity of the estrogen. The compound is stored in the lipid depots of the body and slowly releases its therapeutic effect. Uterine bleeding may be induced by large dosage schedules of the drug and occasionally occurs with smaller doses.

The average dose of chlorotrianisene in the treatment of menopausal symptoms is between 12 and 24 mg. daily by mouth. In prostatic cancer a daily dose of 24 mg. is recommended.

**Methallenestril (Vallestril).** This estrogenic substance differs in structure from the other generally used synthetic estrogens in that it contains a naphthylene nucleus, as shown in the formula.



Methallenestril
Vallestril
[3-(6-methoxy-2-naphthyl)-2,2-dimethylpentanoic acid]

Vallestril is effective as an estrogen upon oral administration. Its action is prompt and produces less gastrointestinal disturbance than stilbestrol. However its potency is only about 1/10 that of the latter drug. The initial dose of Vallestril is 6 mg. daily for 3 weeks and 3 mg. daily thereafter as required.

In general, the actions of the natural and synthetic estrogens are similar. There are differences, however, in potency and also in freedom from undesirable side actions.

**Absorption and excretion of synthetic estrogens.** The synthetic estrogens as a class are available upon oral administration. They are readily absorbed from the gastrointestinal tract and are not inactivated by the liver. Like the natural estrogens they are also available parenterally. They are absorbed also through mucous membranes.

After the administration of diethylstilbestrol, 10 to 30 per cent of the compound is excreted in the urine and in the feces.

**Pharmacologic response of the synthetic estrogens.** Fundamentally the actions of the synthetic estrogens emulate the responses to the naturally-occurring steroids. They have replaced the natural estrogens in therapy to a great extent because of their greater availability upon oral administration and their smaller cost to the patient.

The synthetic estrogens produce undesirable side reactions in some patients. These are *nausea*, *vomiting*, *abdominal cramps*, and *migraine*. Arnold and Hamperl (1939) showed that bone marrow changes, cloudy swelling, and congestion and necrosis of the kidneys, liver, and adrenals could be produced in animals by large doses of diethylstilbestrol.

McShan *et al.* (1947) showed that diethylstilbestrol and certain other synthetic estrogens inhibited the succinoxidase system of rat adrenal, brain, pituitary, lutein, kidney, and heart tissues *in vitro*. It is of interest that the capacity of these compounds to cause estrus is not destroyed when they are used *in vitro* to inhibit the succinoxidase system.

Page *et al.* (1941) were unable to produce carcinoma in rats by the implantation of stilbestrol under the skin.

**Choice of a synthetic estrogen.** *Diethylstilbestrol* was the first generally used synthetic estrogen. It is perhaps for that reason that it is so extensively used today. It is recognized in the United States Pharmacopeia and is relatively inexpensive. The choice of a synthetic estrogen depends mainly upon the frequency and character of the side effects encountered with its administration. It often becomes a matter of tailor-fitting the estrogen to the needs of the patient.

### NATURAL ESTROGENS

**Absorption and excretion.** The estrogens estrone and estradiol are sparingly soluble in water. They are absorbed from the gastrointestinal tracts, however. When administered orally the natural estrogens are inactivated by the liver to a considerable extent. Estradiol is excreted in large amounts in the bile, in addition to the process of liver inactivation. They are therefore much more effective upon parenteral administration. The natural estrogens are absorbed from the intact skin by local application. If they are administered in sufficient quantity, full therapeutic effect may be achieved by this method. The parenteral use of oil solutions is the most common method of administration.

When estrone is injected intravenously, it rapidly disappears from the blood. The nature of circulating estrone has been investigated by Szego and Roberts (1946). They report that an equilibrium between the estrogen and blood proteins is established. More than 60 per cent of the estrogen combines with blood protein. The protein-estrogen appears in the lipo-fraction III-O of Cohn *et al.* (1946). Upon intramuscular injection in oil solution, approximately 20 per cent of the steroid is excreted in the urine conjugated with glycuronic acid (Odell and Marrian, 1936). The excreted conjugate is inactive as such, but activity is restored upon the hydrolysis of the conjugate to the free estrone. Jensen *et al.* (1945) obtained estrone sulfate from the urine of stallions. The naturally-occurring conjugates of the estrogenic substances in urine form the basis of many commercially available estrogenic preparations such as *Premarin, Amnestrogen, Estrifol, Hormestrin, Konogen, and Conestron.*

**Piperazine Estrone Sulfate (Sulestrex Piperazine)** is piperazine estrone sulfate stabilized with a small quantity of free piperazine. Its action is the same as that of the naturally-occurring, water-soluble, conjugated estrogens. The substance is administered orally, usually in doses of 1.5 mg. daily for menopausal symptoms.

Because the estrogens are so rapidly excreted it has been common practice to prepare their esters, such as the benzoate and propionate, for intramuscular use. These are slowly hydrolyzed and provide a longer duration of estrogenic activity.

The soluble conjugated natural estrogens afford a method of using these substances in the management of carcinoma of the breast and prostate. Hertz *et al.* (1949) administered the conjugated natural estrogens by intravenous infusions in doses of 100 to 400 mg. Most of the patients tolerated the estrogens very well. Blood serum levels of from 17.6 to 48 μg./ml. were obtained. The estrogens were excreted within 8 hours.

Other estrogenic substances representing a naturally-occurring estrogen esterified are *estradiol cyclopentylpropionate* (*Depo-Estradiol cyclopentylpropionate*) and *estradiol valerate* (*Delestrogen*). These agents are repository forms of estradiol and may be given by intramuscular injection at weekly intervals or longer. Estradiol cyclopentylpropionate is given in doses of 1 to 5 mg., and estradiol valerate is given in doses of 5 to 20 mg.

**Pharmacologic response to the estrogens.** It has been previously stated that the principal action of the estrogens is to induce estrus. By injections of the estrogens in sexually immature or ovariectomized rats, estrus is rapidly produced. This involves also the development of the accessory female genital system; the uterine tubes and the uterus as well as the vagina are affected. There is no action on the ovaries. Hechter *et al.* (1940) showed that the estrogens produced vasodilatation in the sex organs.

The uterus is made sensitive to oxytocin under the influence of estrone (see page 775). Reynolds (1938) attributed the vasodilatation of the uterus to the liberation of acetylcholine in the organ induced by estrone.

As was stated previously, estrogens act upon the anterior lobe of the pituitary and inhibit the secretion of FSH.

Estrone also stimulates the development of the mammary duct system.

The estrogens have a fairly wide range of safety. In doses 10 times the effective estrogenic dose, estrone is apparently without specific toxic action (Morrell *et al.*, 1930). Repetitious injections may produce hyperplasia and metaplasia of the sex organs such as the uterus and breast. Uterine contractility, long bone growth, and epiphyseal closure have also been encountered.

It is established that the estrogens are carcinogenic agents in certain laboratory animals. Shimkin and Grady (1941) showed a parallelism between the estrogenic activity of these substances and their capacity to produce neoplasms in animals. Zondek (1940) administered tremendously large doses to many women and observed no indication of carcinogenesis. Geist and Salmon (1941) found no indication of carcinogenesis in a large group of patients to whom they administered estrogens. Vaginal and endometrial biopsies were made frequently. In certain instances the total dosage amounted to 53 million international estrogenic units. Novak (1954) states: "Postmenopausal endometrial hyperplasia is associated with and related to carcinoma of the uterine fundus; estrogenic therapy causes hyperplasia of the endometrium, but it cannot be concluded that estrogenic therapy causes cancer because an undefined genetic predisposition seems to be essential." Nevertheless it should be borne in mind that in animals, individual susceptibility to induced cancer varies greatly, and a high degree of susceptibility on the part of any patient should be considered a possibility.

### Estrogens and Atherogenesis

It has been observed that premenopausal women are relatively free from coronary sclerosis. It was considered that this immunity might be associated with the presence of estrogens in the circulation. Stamler and associates (1953) showed that estrogens were effective prophylactically and therapeutically against cholesterol-induced coronary atherogenesis in cockerels. The use of estrogens in the treatment of individuals would naturally be complicated by the possible hazard of the feminizing effects. These investigators showed that in cockerels the estrogenic feminization was prevented by the administration of androgens. The prophylactic inhibition of the cholesterol-induced chick coronary atherogenesis was not antagonized by the administration of androgens.

Steiner *et al.* (1955) used daily doses of 0.25 to 1 mg. of ethinyl estradiol in male patients with coronary artery sclerosis. They observed a definite fall in cholesterol:phospholipid ratio. This prevailed in normal subjects also. The change appeared to be due to the lowering of the serum cholesterol level without appreciable change in the phospholipid levels. The neutral fat levels of the serum increased in 8 of the 10 test periods. Although there was a favorable shift in the cholesterol:phospholipid ratio, the concomitant effects of *fatigue, anorexia, nausea, vomiting, loss of libido,* and *breast tenderness* prohibited prolonged therapy. No lessening of chest pain or improvement in EKG pattern was observed.

Oliver and Boyd (1961) of Edinburgh used ethinyl estradiol in a 5-year study with atherosclerotic patients up to the age of 65. They observed no beneficial effects. On the other hand, Warren and Cheatum (1963) in Chicago used Premarin, a natural estrogen, over the same period in postcoronary patients up to 50 years of age with a matched placebo group and found a statistically favorable survival rate in the treated group. A dosage schedule of 10 mg. daily evoked a favorable response in the blood lipoprotein-lipid pattern. Breast enlargment and loss of potency and libido were the principal untoward effects.

Thus this salient problem of treatment of the arteriosclerotic and postcoronary patient remains polemic. It does appear to the authors that benefit is derived from the treatment, and the early work on the chick with cholesterol-induced atherosclerosis mitigated by estrogens can possibly be extrapolated to man. The unsolved problems appear to lie in the choice of estrogen, the optimal dosage, and the elimination of the feminizing effects. Therefore one awaits the synthesis of such a compound by the chemist which will be devoid of the feminizing activity of estrone and yet retain its anti-atherosclerotic action.

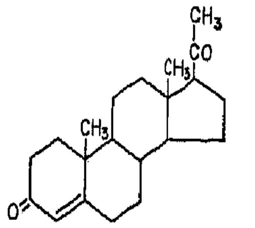
### Hormone of the Corpus Luteum
### Progesterone

The role played by progesterone in the menstrual cycle has been mentioned previously. Its elaboration by the corpus luteum is indicated on the schematic chart of the menstrual cycle (see page 764). The placenta contains 20-$\alpha$- and 20-$\beta$-hydroxyprogesterone, possessing hormonal activity. These are likely metabolites of progesterone.

The ovarian hormones are concerned with the characteristic uterine and vaginal changes which are typical of estrus. The proliferation of the endometrium which is induced by the estrogens is extended by the corpus luteum which elaborates progesterone. Progesterone converts the proliferative phase to the secretory or progestational phase. The proliferation of the endometrial mucosa provides for the attachment of the ovum, should fertilization occur. If the ovum is fertilized, the corpus luteum continues to grow. Its presence appears to be essential for the continuation of pregnancy. The progesterone produced by the corpus luteum suppresses ovulation. It is of interest to note that the progesterone elaborated by the corpus luteum greatly exceeds the levels of estrogen. Approximately 20 mg. are produced daily during the second half of the menstrual cycle and 250 mg. daily during pregnancy, this latter amount largely of placental origin. In late pregnancy the blood levels of progesterone vary from 2 to 15 $\mu$g./100 ml., whereas in nonpregnant women the level is so low that it is scarcely detectable. In the blood, progesterone is linked to plasma proteins and disappears rapidly from the circulation, undergoing metabolism in the liver. The metabolites are excreted as conjugates with glucuronic acid in the urine. The assay methods estimate the mixture of metabolites in the urine as "pregnanediol." During the period of full corpus luteum activity the human ovary produces about 1000 mg. of progesterone daily. The blood level of progesterone may reach 0.5 mg. per cent, whereas that of estrogen seldom exceeds 0.6 $\mu$g. per cent.

Various functions had been assigned to the corpus luteum prior to 1934. But in that year Butenandt succeeded in isolating from the corpora lutea the hormone progesterone. It appears that its physiologic functions in the menstrual cycle and in pregnancy are mainly accomplished by progesterone elaboration.

Progesterone has been prepared from 2 other natural products, stigmasterol, a constituent of calabar bean and soy bean oil, and pregnanediol, an inactive steroid of pregnancy urine. The structure of progresterone is shown in the accompanying formula.



Progesterone, U.S.P.
(pregn-4-ene-3,20-dione)

**Absorption and excretion of progesterone.** Progesterone is not readily absorbed from the gastrointestinal tract. It may be given intramuscularly in 5-mg. doses in oil solution. It is readily absorbed from the vagina. *Anhydrohydroxyprogesterone* is available by oral administration and is given in 5- and 10-mg. tablets.

Progesterone is not excreted in the urine unchanged. It is reduced in the body, principally by the liver, to pregnanediol, conjugated with glycuronic acid, and excreted in the urine. This is found in pregnancy urine and in urine of nonpregnant women during the corpus luteum phase of the menstrual cycle.

Progesterone occurs as a white or creamy white, crystalline powder, which is sparingly soluble in water.

**Pharmacologic response to progesterone.** Progesterone diminishes the spontaneous rhythmic contractions of the uterus and the smooth muscle of the ureter. It renders the uterus less sensitive to the action of oxytocin and ergonovine. This tranquilizing of uterine activity by progesterone is probably necessary for the successful continuation of pregnancy. There is a substantial segment of opinion which opposes this view of the physiologic role of progesterone in pregnancy.

Progesterone injections induce the endometrium to convert the proliferative phase to the secretory or progestational phase. Progesterone also induces proliferation of the secretory elements of the breast. It causes a multiplication in the cornified vaginal epithelium as well.

Progesterone has been said to have an inhibitory effect on the secretion of the gonadotropins of the anterior lobe of the pituitary. Its effect on the pituitary is less pronounced than that of estrone.

Progesterone affects nitrogen metabolism. It has been observed that 50 mg. of parenterally administered progesterone daily for 30 days was accompanied by an increased excretion of urinary nitrogen. There was also a loss of sodium and slight loss of chloride.

**17-Alpha-hydroxyprogesterone Caproate (Delalutin).** Delalutin is a derivative of progesterone which is more potent and longer in its duration of action than progesterone. The progestational activity of Delalutin in rabbits persists from 17 to 20 days after a single subcutaneous injection. This duration of action is 2 to 4 times longer than that of progesterone and twice as marked.

**Dydrogesterone (Duphaston).** Dydrogesterone is a newer derivative of progesterone which is available orally as a progestogenic agent. Chemically the compound is 9$\beta$,10$\alpha$-pregna-4,6-diene-3,20-dione. Dydrogesterone appears to be devoid of toxicity and androgenic or estrogenic activity. No suppression of pituitary activity has been observed in its clinical use. Dydrogesterone is indicated in the same conditions as is progesterone. It differs from the other available progestogens in that it is nonthermogenic.

The compound is available in 5-mg. tablets; the recommended dosage for intermittent therapy is 5 to 10 mg. daily from the 5th to 25th day of the menstrual cycle. The dosage for continuous therapy is 5 to 30 mg. daily.

**Medroxyprogesterone Acetate (Provera).** Medroxyprogesterone acetate is an orally available progestogenic agent derived from progesterone. Chemically it is 6 $\alpha$-methyl-17$\alpha$-acetoxyprogesterone. The compound, unlike progesterone, is highly active upon oral administration. The agent is devoid of estrogenic or androgenic activity and does not cause suppression of adrenal or pituitary activity. Occasional somnolence appears to be the only side effect encountered from the use of medroxyprogesterone. The indications for the agent are the same as those for progesterone.

The drug is available in 2.5- and 10-mg. tablets. The dose recommended for withdrawal bleeding in functional amenorrhea is 2.5 to 10 mg. daily for 5 to 10 days on the assumed 16th to 21st day of the menstrual cycle. Larger doses of 10 to 40 mg. daily are given in threatened abortion.

### SYSTEMIC CONTRACEPTIVES

The awareness of the expanding population of the earth, which is increasing by the alarming number of about 50 million people annually, has lent impetus to the search for systemically-active contraceptives. Substantial progress has been made in the development of steroidal compounds related to progesterone. In the United States there are 2 progesterogens approved as oral contraceptives. They are *Enovid* and *Ortho-Novum*. Each is a 19-nortestosterone steroid and closely related chemically. Enovid, or norethynodrel (17$\alpha$-ethynyl-17-hydroxy-5-[10]-estren-3-one), is approved by the FDA for oral contraception in 5- and 10-mg. doses. Each 10-mg. tablet of Enovid contains 9.85 mg. of norethynodrel and 0.15 mg. of an estrogen, ethynylestradiol 3-methyl ether. Ortho-Novum, or norethindrone (17$\alpha$-ethinyl-17$\beta$-hydroxy,19-norandrost-4-ene-3-one), is approved by the FDA only in a 10-mg. dose. Each 10-mg. tablet contains 0.06 mg. of 3-methoxy ethinyl estradiol.

In addition to these 2 progestogens, several others are being studied experimentally but as yet are unapproved. Among the more promising is *norlutin* acetate. These agents are capable of inhibiting ovulation but do not usually prevent menstruation if administered cyclically.

For contraception, 5 mg. of Enovid or 10 mg. of Ortho-Novum per day ordinarily is prescribed. The patient begins taking the compound on the fifth day of her menstrual cycle, counting the first day of the menses as day 1. She takes 1 tablet daily for 20 consecutive days and stops. The drug is often prescribed to be taken with the evening meal; this timing lessens the likelihood of nausea and spaces the doses 24 hours apart. If these drugs are taken by the patient precisely as prescribed, the chances of pregnancy are negligible. For example, Goldzieher *et al.* (1962) reported on their observations with Ortho-Novum on 6139 cycles in 210 women. They state, "Since the inception of this study there has not been a single unplanned pregnancy."

Although thrombophlebitis has been observed in some patients on Enovid therapy, an actual causal relationship does not appear to be established. Ortho-Novum has not been incriminated in this regard, and if these progestational agents cause thrombophlebitis, one might expect each to induce the condition. Another factor to be considered is that Enovid has been used as a contraceptive for a much longer period than Ortho-Novum.

Pincus *et al.* (1961) reported success with a new potent oral inhibitor of ovulation. Their compound is Ethynodiol (17$\alpha$-ethinyl-4-estrene-3-5-diol) diacetate. In their studies Ethynodiol was effective in daily doses of 1 mg. with estrogen with minimal side effects.

Other pharmacologic approaches are being made toward the control of human fertility. These approaches are with nonsteroidal compounds. Among these approaches, which are at present in the experimental stage, are (1) a pyrrolidine derivative that inhibits implantation of the ovum; (2) a thiocarbamylhydrazine derivative that inhibits ovulation; and (3) N,N′ bis(dichloracetyl)-1,8-octanediamine, which inhibits spermatogenesis when administered to the male.

Extensive clinical trials with the agents that inhibit ovulation, first in densely populated areas of the world such as Japan and Puerto Rico, and now in the United States, testify to their effectiveness. Results have been promising. It is clear that such studies involve many socioeconomic factors as well as the reliability of the drug. At present a great barrier to success is the expense involved in treatment and the failure of the patient to cooperate. A factor of paramount importance is the long-term effect of such agents administered for long intervals during the child-bearing years of the woman. The question of conception (which in some cases may be desirable) after years of medication with the contraceptive has been answered in the affirmative. Progress is tortuous in this field, but it is being made despite innumerable difficulties. The ultimate value of this type of investigation to the life and happiness of mankind on this earth cannot be overestimated. Pincus (1959) very cogently comments: "If we are on the brink of finding numerous methods for the inhibition or disruption of various stages of the reproductive processes, it means that we are also armed with means of repair of natural defects. Fertility and sterility are two sides of the same coin."

### THERAPEUTIC USES OF THE ESTROGENS AND PROGESTERONE

**The estrogens.** The principal use of the estrogens is in *the treatment of menopausal symptoms*. For this purpose combined estrogen-androgen therapy is often employed (see page 783).

Estrogens are also useful in the treatment of postmenopausal conditions such as *senile vaginitis*, *kraurosis vulvae*, and *pruritus vulvae*. The estrogens have been found useful in certain cases of *functional uterine bleeding*. *Gonorrheal vaginitis* in children often responds to estrogen therapy. In the treatment of *hypogenitalism* in the female the estrogens are of some value. They are not a stimulant to normal ovarian function but merely serve as substitution therapy.

The estrogens are useful in the treatment of prostatic cancer (see page 910) and in the control of hemorrhage (see page 712).

The principal use of the estrogens, as stated previously, is in the mitigation of the disconcerting symptoms of menopause. For this purpose the following suggestion is noteworthy: avoid the use of diethylstilbestrol or any other estrogen unless the symptoms are clearly menopausal and constitute a real problem to the patient.

**Progesterone.** The principal therapeutic use of progesterone is in the treatment of *functional uterine bleeding*, *amenorrhea*, and *infertility*. The availability of anhydrohydroxyprogesterone and other derivatives orally makes the treatment a great deal more feasible than with the intramuscular injections of progesterone.

Progesterone is used also in cases of repeated abortion. Although progesterone and the other progestogenic agents are used extensively for this purpose, their absolute value has not been proved. There also remains the risk of the masculinization of the female fetus by the administration of progestogenic agents.

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# 49

# *The Pharmacologic Responses of the Reproductive System to the Androgens*

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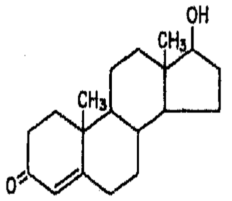
The influence of the testes on the primary and secondary sexual characteristics has been a matter of common knowledge for many years. The fact that the testes exert their effect through the elaboration of hormonal substances was established comparatively recently. Koch *et al.* (1929) made extracts of the testes of bulls and demonstrated their capacity to produce marked effect when injected into capons. The most striking response was the stimulating effect on the growth of the comb. The effect on the comb growth appeared so consistently that Koch used it as a method of biologic assay for the measurement of potency of testicular extracts. The unit of measurement of activity established by Koch is designated as the "capon unit." It is the amount of testicular substance which, when injected daily for a period of 5 days, will produce an average increase of 5 mm. in length and height of the combs of at least 5 brown Leghorn capons.

**The male sex hormones.** There are at least 5 steroidal hormones which exhibit a typical androgenic activity when measured on the capon comb growth test. All are derivatives of androstane. The most potent by far is testosterone, shown in the formula.



Testosterone

Of the other compounds which approach the activity of testosterone, androsterone is the most potent, having approximately ⅐ of the activity of testosterone.

Butenandt (1931) isolated the first male hormone, namely, androsterone. He obtained 15 mg. of the crystalline steroid from 15,000 L. of urine. It has been estimated that urine contains approximately 1 mg. per L. of androsterone. When subjected to the biologic assay procedure using the capon, 150 to 200 μg. of androsterone are equal to 1 capon unit.

Working with a comparatively small sample of androsterone, Butenandt established the structure for the steroid. In 1934 Ruzicka succeeded in preparing androsterone from cholesterol and established the correctness of the Butenandt formula.

Butenandt further obtained dehydroisoandrosterone from urine. This second hormone is present in urine in about the same concentration as is androsterone. The activity of dehydroisoandrosterone is from ⅓ to ½ that of androsterone. It is of interest that dehydroepiandrosterone has been isolated from the urine of pregnant and nonpregnant women. Its structure resembles quite markedly the structure of estrone (see page 768).

**Isolation of testosterone.** The 2 hormones androsterone and dehydroisoandrosterone did not appear to be as active as androgens as some of the testicular extracts which Koch had prepared. It was therefore suspected that there existed at least one other hormone which was more active than either of these substances. Laqueur *et al.* (1935) pursued this lead. If proved to be correct. These investigators succeeded in isolating from testes the potent testicular hormone testosterone. From 100 kg. of testes they obtained 10 mg. of the steroid. Comparing the activity of testosterone with that of androsterone on various test animals, the following comparisons were obtained: by the capon test, testosterone was 6 to 10 times as active as androsterone, on castrate rats testosterone was shown to be 25 to 30 times more active than androsterone in stimulating the seminal vesicles.

**Physiologic considerations.** The testicular hormone, testosterone, is not excreted in the urine. The androgenic substances in male urine, such as androsterone and dehydroepiandrosterone occur in urine as conjugates with glycuronic acid. It is of interest that when injected testosterone is excreted in the urine as androsterone (Dorfman *et al.*, 1939).

Other androgenic substances are excreted in the urine in diseases of hyperactivity of the adrenal cortex. It will be observed (see page 829), that the principal hormones from the adrenal cortex are closely related to the androgens chemically.

**Pharmacologic responses to testosterone.** Testosterone, made synthetically from cholesterol, became available shortly after its isolation from testes. This substance, when administered to castrate male animals or human beings, removes the changes affected by castration and restores them to normalcy. It is an example of substitution therapy.

Testosterone does not stimulate spermatogenesis; it appears to be necessary for its maintenance. Large doses of testosterone evoke a suppression of spermatogenesis, after which, however, there usually follows a rebound, as evidenced by a sperm count higher than the pretreatment level. Like the estrogenic substances and progesterone, it inhibits the secretion of the anterior pituitary gonadotropins (Moore, 1935). Breast hypertrophy in the male is antagonized by the injection of testosterone. Testosterone and its derivatives have been found useful in treatment of advanced metastatic carcinoma of the breast (see page 910). Testosterone assists in bringing about the descent of the testis in cryptorchidism. It appears, however, to be less dependable than the chorionic gonadotropin. Testosterone may cause prostatic hyperplasia. This effect is antagonized by the estrogens.

In females, testosterone acts to some extent like progesterone. It tranquilizes uterine activity and renders the myometrium less sensitive to the oxytocic principle of the posterior pituitary. Testosterone tends to suppress estrus by its inhibitory effect on the anterior lobe gonadotropin secretion.

The androgens have been shown to affect nitrogen metabolism. The administration of testosterone provokes a reduction in urinary nitrogen excretion. The nitrogen retained by the action of testosterone probably goes into the formation of tissue proteins.

Occasionally testosterone may produce jaundice (Wood, 1952). The blood cholesterol esters are reduced. There is no increase in serum alkaline phosphatase, decrease in serum proteins, or change in the flocculation tests. The histologic picture shows the bile pigments plugging the intercellular canaliculi without cellular necrosis.

**Testosterone at a cellular level.** Eisenberg *et al.* (1949) showed that testosterone inhibits the oxygen uptake of rat brain, liver, and striated muscle. The action appeared to be specific for testosterone and not general among steroidal compounds. The primary site of inhibition is likely to be at the dehydrogenase level of the main line of biologic oxidation, since the inhibition of glucose oxidation is not reversed by methylene blue.

Endahl and Kochakian (1959) studied the action of testosterone upon the enzymes of the Krebs' cycle. The enzymes of the cycle diminish their activity after castration concomitant with a decrease in protein synthesis. Upon the administration of testosterone an increase in activity occurred with increased protein synthesis in the heart of the mouse and rat and in the temporal muscle of the guinea pig. Since most of these enzymes are present in the mitochondria, it appears that testosterone evokes the synthesis of mitochondrial constituents simultaneously with the synthesis of other protein constituents of the particulate tissue.

When radioactive testosterone is incubated with benign hyperplastic human prostate, a number of steroid metabolites are formed, suggesting the presence of 2 steroid dehydrogenases in the tissue: (1) a 4,5-reductase, and (2) a less common 6-hydroxylase. The principal metabolites are dihydrotestosterone and androstanediol; each evokes androgenicity comparable to testosterone. Farnsworth and Brown (1963) pose an interesting question concerning this study: "Is the parent steroid a definitive stimulus or a precursor to which the gland is able to adapt, through metabolic transformation, to its particular needs?" It appears to us that in the prostate, testosterone serves as a precursor of the other androgens of comparable activity.

In the intact animal testosterone is reversibly bound by serum proteins without the formation of metabolites (Wotiz *et al.*, 1955). After release of the testosterone, enzyme degradation of the steroid molecule occurs.

**Testosterone Propionate, U.S.P.** Testosterone propionate is a white or slightly yellow, crystalline powder. It is odorless and stable in the air. The ester is insoluble in water but soluble in oils.

The esterification of testosterone prolongs its action. Although the substance is active by mouth, the oral effective dose is about 10 times the intramuscular dose. Therefore, the intramuscular injection of the oil solution is the preferable method of administration. The average dose is 25 mg.

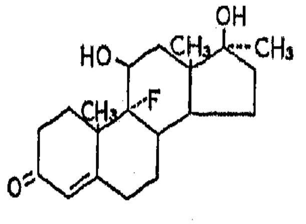
In order to achieve prolongation of action, certain modified esters of testosterone are employed. One of these is *testosterone cyclopentyl propionate*, which is available in oil solution containing 50 or 100 mg. of the ester in 1 ml. Another product is *testosterone phenylacetate*. Reifenstein *et al.* (1954) found that upon depot injection testosterone propionate reached its peak activity in 5 days, testosterone cyclopentyl proprionate in 10 days, and testosterone phenylacetate in 15 days. There appears to be clinical advantage to the prolongation of action characteristic of these newer testosterone esters.

Testosterone propionate is available under many trade names such as *Andronate*, *Masenate*, *Neo-Hombreol*, *Oreton*, *Synandrol*, *Synerone*, *Perandren*, and *Testodet*.

**Methyltestosterone, U.S.P.** The responses to testosterone and methyltestosterone are essentially the same. Methyltestosterone is available for oral and sublingual administration. Orally the dose of methyltestosterone is 3 to 5 times that of testosterone propionate given intramuscularly. Absorption from the buccal membranes is more effective than absorption from the gastrointestinal tract. Sublingually the dose is ½ to ⅔ of the oral dose. Methyltestosterone is also absorbed percutaneously by inunction of an ointment; the usual strength of the ointment is 2 or 4 mg./gm.

Methyltestosterone is available under many trade names such as *Metandren*, *Neo-Hombreol (M)*, and *Oreton-M*.

**Other androgens.** Although many synthetic estrogens have been available in therapy for years, methyltestosterone was the only synthetic androgen in general use until recently. A number of compounds related to testosterone have been synthesized and certain of these were found to exceed methyltestosterone in *androgenic* and *anabolic* activity. Of the compounds studied fluoxymesterone appeared to be the most promising. Its structure is shown in the formula:



Fluoxymesterone
Halotestin, Ultandren
(9α-fluoro-11β-hydroxy-17α-methyltestosterone)

Fluoxymesterone is a crystalline powder which is insoluble in water. It is soluble in ether and other organic solvents.

*Pharmacologic response to fluoxymesterone.* When fluoxymesterone was administered orally to rats it was found to be 10 times more potent than methyltestosterone in stimulating the seminal vesicle (androgen activity). It was about 20 times more potent than methyltestosterone in anabolic activity. In the adrenalectomized rat fluoxymesterone elicited no evidence of sodium retention. The $LD_{50}$ in the mouse of fluoxymesterone is greater than 1000 mg./kg. upon intraperitoneal injection. No evidence of toxicity or visceral damage was evoked by fluoxymesterone after 3 weeks of oral administration to young male and female rats.

*Clinical use of fluoxymesterone.* It does appear that fluoxymesterone provides complete replacement therapy in hypogonadal males. The effective oral dose supporting sexual activity ranges from 2 to 20 mg. daily, with an average of 5.5 mg. The equivalent response with methyltestosterone was achieved with an average daily dose of 24.6 mg.

Nitrogen and electrolyte balance studies in patients to whom fluoxymesterone was given indicate an activity about 5 times greater than that of methyltestosterone. The side effects elicited by fluoxymesterone are similar to those elicited by testosterone. No cases of jaundice have been reported. Like all other androgens, fluoxymesterone is contraindicated in prostatic cancer.

The greater potency of fluoxymesterone over methyltestosterone in patients with eunuchism and hypogonadism has been demonstrated.

**Therapeutic use of testosterone.** Testosterone is used effectively in the treatment of *hypogonadism.* This condition results from a diminished quantity of testosterone secreted into the blood by the testes. The absence of testosterone caused by traumatic or surgical removal of the testes produces the complete eunuch state. In each of the conditions testosterone may produce striking symptomatic improvement, such as disappearance of effeminacy and enlargement of the phallus, scrotum, prostate, and seminal vesicles. Atrophy of the accessory male structures which occurs in the eunuch state may be checked with the administration of testosterone by continual substitution therapy.

For substitution therapy in hypogonadism testosterone propionate may be injected in doses of 5 to 25 mg. 3 times a week. Orally the dose of methyltestosterone required is about 3 times greater. It is most satisfactory to administer methyltestosterone daily. If it is possible for the tablets (linguets) to be absorbed from beneath the tongue the efficiency is increased, and from ⅓ to ½ of the steroid may be used.

The untoward side effects of testosterone are few and mild. If dosage is kept within specified limits, in the majority of cases there are no untoward side effects experienced. *Priapism* is one of the most frequently encountered side effects. Generalized puffy edema and precordial pain have resulted from excessive dosage.

Testosterone has been employed in the treatment of the symptoms of the *male period of involution.* Most individuals pass through the period asymptomatically. Others may be benefited by androgen therapy. The blood testosterone level follows a curve beginning at puberty and ascending to its highest level between the ages of 22 and 25 years. This height is maintained from 5 to 10 years and then slowly declines. The decline becomes sharper in the fifth decade, and at 60 it approaches the prepuberal level.

Vasomotor disturbances such as occur in the menopause may be experienced. Headache, excessive fatigue, nervous irritability, and indecision are frequent symptoms. Many observers have found testosterone of definite value in the relief of these symptoms. Undoubtedly in this type of therapy with the androgens there exists a strong psychogenic component which must be taken into consideration in evaluating the patient's subjective improvement.

Testosterone appears to be used extensively in the treatment of the *menopausal syndrome*, combined with estrogens. The estrogens and androgens are additive in their suppression of the overactive gonadotrophic function of the pituitary. Estrogen dosage may therefore be reduced accordingly. The combination therapy, as a rule, elicits a smoother transition from a reproductive to a nonreproductive physiology. Glass and Shapiro (1951) studied 92 menopausal women on estrogen, androgen, placebo, and estrogen-androgen therapy. Seventy-three of these patients remained freer from subjective symptoms on the combination therapy. They employed 0.25 mg. of diethylstilbestrol with 5 mg. of methyltestosterone. Many combination preparations of this kind are now available.

Testosterone is used in the treatment of *functional uterine bleeding.* It has been stated that testosterone acts upon the uterus in a manner somewhat similar to that of progesterone. Progesterone is useful in the treatment of functional uterine bleeding, and testosterone also has been employed with success. In cases that have failed to respond to progesterone treatment, testosterone has sometimes been valuable (Novak, 1946). When the dosage of testosterone is too high or continued for excessively long periods of time it may produce hirsutism and other manifestations of masculinization. These symptoms do not occur when the dosage is kept under a 1-month total of 200 mg.

Owing to their anabolic activity and their capacity to retain calcium, the androgens have been used with success in the treatment of *osteoporosis* and *osteomalacia* in elderly patients. Testosterone propionate is administered in 10- to 25-mg. doses intramuscularly each week for 1 month. The dose is then reduced to ½ at weekly intervals for 2 months and then to 1 monthly dose for a year. A diet high in protein is a valuable adjunct to treatment (Steinmann, 1958)

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# 50

# *Pharmacologic Agents and the Treatment of Dysmenorrhea*

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The use of drugs in the treatment of dysmenorrhea vies in volume with the use of drugs in the treatment of headache, upper respiratory affections, and constipation. The problem is one of special concern to the gynecologist. In private practice limited to gynecology and obstetrics, dysmenorrhea was found as a primary diagnosis in 4.6 per cent of 8160 consecutive patients (Bickers, 1954). In addition, the use of scores of proprietary remedies used without medical advice in the treatment of painful menstruation is of medical concern. It is estimated that approximately 175 million hours are lost from work annually owing to dysmenorrhea. This corresponds to the total loss of a year's work by 75,000 women.

## NATURE OF DYSMENORRHEA

Menstruation, like all excretory functions, is usually accomplished without discomfort. However, there are women whose adolescence and youth are plagued by recurring episodes of disabling symptoms. Such distress in otherwise healthy young girls without organic pelvic disease is *primary dysmenorrhea.* Painful menstruation occurring some years after the menarche and associated with pelvic pathology such as leiomyoma, endometriosis, and endometrial polyp is *acquired dysmenorrhea.* In this discussion of the use of drugs in the treatment of dysmenorrhea, the subject will be confined to so-called *primary dysmenorrhea.*

The average age of the menarche in America is 13.5 years. When dysmenorrhea complicates the menstrual function, it usually begins some 6 to 12 months after the menarche. Dysmenorrhea is only experienced when the ovulatory cycles are established.

Primary dysmenorrhea is not a clinical entity; it is a symptom complex in which *uterine cramps, nervous tension and irritability, breast fullness and tenderness,* and *low abdominal and back pain* contribute in varying degrees to the patient's discomfort. *Intermittent, spasmodic cramps* is the major symptom. Cramping usually occurs synchronously with the onset of menstruation but may precede it by some hours. The dysmenorrheic symptom complex is a triad: premenstrual tension related to abnormal water storage during the premenstrual week; cramps related to abnormal patterns of uterine contractions; and pelvic vascular congestion related to blood and lymph stasis in the pelvic, vascular, and lymphatic beds.

**Etiology.** The cause of dysmenorrhea is unknown. In all probability there is no single cause, but certainly much of the pathologic physiology that is known can be explained on the basis of autonomic nerve imbalance. The cramping pains arising from disordered, dyskinetic myometrial contraction patterns represent either an intrinsic defect in the muscle fibers themselves or a failure on the part of the autonomic nervous system to establish a rhythm of contractility that will permit accommodation to the stretch of desquamated menstrual debris within the cavity. Likewise, autonomic nervous system imbalance may contribute to abnormal water storage during the premenstrual week and atony and congestion in the pelvic and lymphatic system of the pelvis.

The menstrual cramps occur when the myometrium is called upon to expel a thick, succulent, highly vascularized, secretory endometrium which has grown under the stimulation of estrogen and progesterone from the corpus luteum. Primary dysmenorrhea occurs only in cycles where there is an actively functioning corpus luteum. Thus the symptom complex of dysmenorrhea occurs only in patients who have ovulated and who menstruate from a well-developed secretory phase endometrium. This implies a normal pituitary-ovarian-endometrial axis. It may be stated, therefore, that primary dysmenorrhea is seen only in patients who are essentially normal from a gynecologic and endocrinologic standpoint. Patients with anovulatory menstruation suffer no pain with the flow, nor do they suffer premenstrual tension or symptoms related to pelvic vascular and lymphatic congestion. If this is the case, why do not all women who ovulate suffer dysmenorrhea?

Patients with dysmenorrhea shed and expel the desquamated endometrium and other menstrual debris with difficulty. For some reason the uterine muscle is unable to adapt to the expanding foreign body of depleted endometrial tissue within the uterine cavity, and the contractions become hypertonic, dysrhythmic. The ordered gradient of intracavitary pressures from fundus to cervix is reversed by the disordered arrangement of pressure gradients within the cavity. When finally the laboring uterus sweeps the uterine cavity clean of its debris and its distending foreign body is eliminated, menstrual cramps promptly disappear.

The uterus of dysmenorrheic patients is different from the uterus of a sister who menstruates painlessly. Experimentally it is possible to reproduce dysmenorrhea in all patients by artificial distention of the uterus with a small intracavitary balloon. In patients with habitual dysmenorrhea the pain is readily induced with distention of as little as a 0.5 ml. volume in the balloon. In other words, these uteri adapt poorly and a disordered pattern of contractions is set up with relatively little distention, as has been repeatedly recorded on the uterograph. In patients who habitually do not have dysmenorrhea and menstruate with a well organized contraction pattern, tension in the cavity may be carried to 2 ml. or 3 ml. before pain is experienced.

It may be postulated that *menstrual cramps are comparable to pain arising in any hollow viscus which is attempting to expel a foreign body disproportionately large for its lumen or adherent to its wall.*

**Premenstrual tension.** Menstruation rarely appears unannounced. It is heralded in most women by *breast fullness*, a *sense of anxiety*, and *nervous irritability*. In some patients, suffering is so intense that *nervousness, fatigue, headache, breast and abdominal fullness, low back pain*, and even *personality changes* of a mildly antisocial nature are nearly incapacitating. These symptoms are directly related to tissue edema.

Positive water balance during the premenstrual week is normal. The average young woman during the 5 to 8 days premenstrually will gain 0.5 to 0.75 kg. in weight, which is interstitial water. This is promptly lost by the physiologic diuresis which occurs on the first day of menstruation. This water retention is thought to be related to high estrogen-progesterone levels at this time. The water retention is an exaggeration of the norm, possibly related to allergic sensitivity to progesterone.

Symptoms occur only in the presence of a normal pituitary-ovarian-endometrial cycle. Estrogen and progesterone from a corpus luteum are essential precursors to the syndrome. The severity of symptoms is roughly related to the amount of water retained. Water storage in excess of 1.5 kg. usually produces very disturbing symptoms, and the occasional patient with a premenstrual weight gain exceeding 2.3 kg. is partially or totally incapacitated. Premenstrual weight gain up to 5 kg. owing to water storage has been reported. Most of these symptoms are relieved by the diuresis associated with menstruation.

**Pelvic vascular congestion.** Heaviness and weight in the pelvis exaggerated during the premenstrual week is a preeminent symptom. The sense of fullness and pressure in the pelvis leads to dyspareunia. Menses are often prolonged and excessive. The uterus upon examination is usually found to be retroverted, enlarged, and tender. Fullness in the broad ligaments suggests dilated veins and venous stasis. The cause of this congestion is unknown but it nearly always occurs in highly emotional, neurotic women. Whether this be the exciting cause of the neurosis or secondary to it has not been determined. It is undoubtedly related to an imbalance in the pelvic autonomic nerve supply.

Besides these factors it is well established that dysmenorrhea in many patients involves a strong psychogenic component.

### TREATMENT OF PRIMARY DYSMENORRHEA

**General procedures.** The principal symptom of dysmenorrhea is pain. During the acute attack, rest in bed and the application of an electric pad or a hot water bottle to the lower abdomen is helpful. The evacuation of the bowels may also bring relief. Bed rest is most important.

**Analgesics.** Mild analgesics are often useful in mitigating the pain of dysmenorrhea. Aspirin and acetophenetedin serve well for mild cases. These drugs are generally given at 3-hour intervals in doses of 0.3 gm. each.

If the pain is too severe to be relieved by these analgesics, codeine phosphate is indicated. For relief of dysmenorrheal pain 60 mg. of codeine phosphate every 3 hours is generally necessary. The use of alcohol and morphine for analgesic effect in dysmenorrhea is definitely interdicted because of the danger of habituation.

**Sedatives.** Analgesics are generally more effective when administered with a sedative. Dysmenorrheal pain may produce marked malaise and nervousness. Phenobarbital is especially helpful during the acute attack. As a rule 30 mg. with aspirin or acetophenetidin every 3 hours will produce sufficient sedation to tranquilize the patient without evoking undue drowsiness.

**Diuretics.** The release or prevention of abnormal water storage during the premenstrual days relieves most of the symptoms of premenstrual tension. By reducing pelvic edema the myometrium functions more efficiently at its task of depleting and excreting the desquamated endometrium, and thus cramps may be partially relieved. However, the most significant symptomatic relief which diuretics brings is relief of the breast fullness and tenderness and of nervous irritability.

For years the acidotic diuretic ammonium chloride (see page 811) has been used for this purpose. Bickers and Woods (1951) observed that the use of pyrilamine (antihistaminic) combined with 8-bromotheophylline was useful in relieving premenstrual tension. Animal experiments and clinical experience indicated that 8-bromotheophylline was the compound responsible for the diuretic activity. This compound is capable of consistently producing diuresis in the presence of vasopressin in animals and man. The theophylline derivative is available as a mixture consisting of 2-amino-2-methyl-1-propanol 8-bromotheophyllinate and pyrilamine maleate in a 5:3 ratio. The mixture is called *neo-Bromth* and is available in tablets containing 80 mg. The recommended dosage is 2 tablets morning and evening daily for 7 to 10 days before the onset of menstruation. This diuretic does not deplete the normal water storage but does effectively block abnormal water retention during the premenstrual week.

The anti-vasopressin effect of 8-bromotheophylline is enhanced by the presence of the antihistaminic in the mixture. This is especially interesting in the light of recent work which suggests that abnormal water storage may be caused by an allergy to progesterone or its products of metabolism. Furthermore, the vascular lymphatic congestion may be an allergic manifestation. In this case the antihistaminic also is of value. If allergy to the progesterone metabolites is a factor in the etiology of the dysmenorrheic symptom complex, then the antihistaminics could conceivably prevent or relieve vascular congestion from abnormal water storage while the bromotheophyllinate relieves the edema.

Bickers and Woods (1952) found that the average premenstrual weight gain in one group of patients before neo-Bromth treatment was 2 kg. and that during the treated cycles the average weight gain for this group was 0.7 kg.

It follows that other diuretic drugs are useful in the treatment of premenstrual tension phase of dysmenorrhea. For example, acetazolamide (Diamox) (see page 803), chlorothiazide (Diuril) (see page 797), and hydrodiuril (Esidrix) (see page 800), are all useful diuretics in the treatment of premenstrual tension.

**Spasmolytics.** The number of uterine spasmolytic drugs used in the treatment of dysmenorrhea is legion. These may be conveniently divided into 2 classes: first, the cholinergic blocking agents are used, such as atropine and synthetic drugs similar to atropine (see page 601); second, the adrenergic agents such as ephedrine and amphetamine, are also used, with limited success. The spasmolytics as a class have been disappointing in the treatment of primary dysmenorrhea.

The cholinergic blocking agents which are highly efficacious for the relief of gastrointestinal smooth muscle spasm have been erroneously presumed to have similar effects upon the myometrium. The myometrial muscle fiber does depend for the regulation of its contractility upon the autonomic nervous system to the same degree as does gastrointestinal muscle. The smooth muscle of intestinal tract is directly under the influence of the autonomic nervous system. The myometrium is only modified by neuromuscular impulses. Intrinsic motility of the myometrium largely determines its contraction pattern.

Most important, a complete spasmolytic would be undesirable in the treatment of dysmenorrhea. Abolition of uterine contractions would not necessarily be followed by pain relief. The uterus needs the normal contraction pattern of relatively high amplitude occurring about 1 per minute, superimposed on low tonicity with a gradient of intracavitary pressures from fundus to cervix, in order to efficiently sweep its endometrial debris into the cervical canal and thus rid the uterus of its distending foreign material.

Indeed, if one accepts the hypothesis of Woodbury *et al.* (1948) that agents effective in the relief of menstrual pain must elicit a definite anti-vasopressin effect on the uterus, the explanation for the failure of the spasmolytics becomes evident. Atropine and its congeners antagonize the motor action of histamine and acetylcholine on the uterus, but histamine and acetylcholine do not give rise to experimental dysmenorrhea, as shown by Woodbury (1949).

**Estrogens.** Primary dysmenorrhea seldom occurs in women during the absence of ovulation. Sturgis and Albright (1940) attempted to inhibit ovulation by the administration of estrogens and thus diminish menstrual pain. The suggested plan to inhibit ovulation is to administer rather large doses of oral estrogen, beginning on the first or second day of menstruation, and continuing for 15 or 16 days, *i.e.*, until after the usual time for ovulation. A nightly dosage of 5 mg. of diethylstilbestrol rarely fails to accomplish this and to make the next period painless. This plan is apt to be ineffective if continued for more than 2 months, and patients should be warned that it may produce minor disturbances of menstrual rhythm. In spite of its limitations and the fact that it can be applied in only an interrupted fashion, this plan appears to be more frequently successful than any other hormonal treatment of dysmenorrhea.

Acquired dysmenorrhea owing to endometriosis has been treated by the complete suppression of menstruation for 3 months with larger doses of diethylstilbestrol. This usually requires 25 mg. daily for 3 months. Should "break through" bleeding occur while the patient is on this dose, it is increased in stair-step fashion by 25 mg. up to a maximal dose of 100 mg. daily. Endometriosis implants will disappear under this therapy, and all symptoms related to the dysmenorrhea are effectively abolished. However, the endometriosis returns immediately upon withdrawal of treatment.

**Progesterone.** Since Novak and Reynolds (1939) demonstrated the inhibitory properties of progesterone on the rabbit uterus, it has been presumed that it would be effective in relieving the hypermotility associated with dysmenorrhea. Such is not the case since progesterone increases the tissue mass of the endometrium, thus providing a larger mass of desquamated tissue and debris within the cavity for a poorly adapting myometrium to expel.

**Testosterone.** On the assumption that testosterone was anti-estrogenic, it has been employed in the treatment of dysmenorrhea. It is not anti-estrogenic in the sense that it neutralizes the estrogen-induced contraction pattern of the myometrium, nor is it anti-estrogenic in its effect upon the endometrium. It has been shown to have little value in the treatment of dysmenorrhea.

**Lututrin (Lutrexin).** Lutrexin is a water-soluble, nonsteroid uterine relaxing factor isolated from the ovaries. It is protein-like in chemical composition. It is similar to "Relaxin" studied by Hisaw (1929 *et seq.*). The uterine activity of Luxtrexin was investigated by Felton *et al.* (1953) and its uterine assay was developed by Krantz *et al.* (1950).

The relation of Lutrexin (see page 759) to the relief of experimentally produced dysmenorrhea has been studied, using nonpregnant women and virgin guinea pigs. Uterine activity was recorded by means of inserted uterine balloons. The effectiveness of the uterine-relaxing factor in markedly reducing or completely obliterating the uterine spasm following vasopressin injection has been clearly indicated. The oral administration of Lutrexin powdered extract, 4 mg./kg. to nonpregnant women 45 to 60 minutes before injection of 2.0 units of vasopressin intravenously will markedly reduce uterine spasm. The vasopressin blocking effect is evident immediately following the intravenous administration of the uterine-relaxing factor to the guinea pig. The spasmolytic activity of Lutrexin in the guinea pig is not limited to vasopressin but is effective, by intravenous administration, against the oxytocic activity of oxytocin. These data are of special interest when viewed in the light of Woodbury's findings (1947).

Rezek (1953) treated 298 clinical cases of dysmenorrhea with Lutrexin. Complete relief was secured within 15 minutes in approximately 70 per cent of the patients with normal endometrium. The drug was given orally with an initial dose of 3000 units (2.5 mg./kg.). Patients with hypoplastic endometrium appeared to respond less well. No undesirable side effects of any kind were noticed, although some patients were observed for as long as 11 menstrual periods. Jones and Smith (1954) reported a study in which 90 women complaining primarily of painful menstruation were treated with Lutrexin. Of these 90 cases 61 had satisfactory relief of symptoms with administration of 1000 to 3000 units (1 to 2.5 mg./kg.), followed by 1000 units every 2 to 4 hours. The fact that a number of women obtained no relief from small doses but adequate relief when larger amounts of the uterine-relaxing factor were administered leads these investigators to believe that the action is physiologic rather than psychologic. The rapid absorption of Lutrexin from the gastrointestinal tract and its prompt relief of pain in most of the cases reported warrant a definite place for this drug in the treatment of dysmenorrhea. Lutrexin is used also in the treatment of premature labor (see page 759).

**Miscellaneous drugs used in dysmenorrhea.** Vegetable extractive preparations are still extensively used in the treatment of dysmenorrhea. Tons of vegetable drugs are grown each year expressly for this purpose. Although these products have through the years been deleted from the Pharmacopeia, the National Formulary recognizes a number of these drugs. Among these drugs used in quantity today are viburnum and hydrastis.

The actual value, if any, of these vegetable drugs in the form of their extractive preparations has never been definitely established in the treatment of dysmenorrhea. Although many of the vegetable extracts do produce relaxation of animal uterine strips and also of human uterine strips, it appears in the light of recent work that this cannot be considered *prima facie* evidence of their value in the treatment of dysmenorrhea. There is undoubtedly an important psychogenic factor involved in their use.

Nicotinic acid has been used with some degree of success in the treatment of dysmenorrhea. The rationale of its use is based upon its capacity to produce capillary dilatation and to relieve uterine ischemia. The adrenergic blocking agent tolazoline (Priscoline) has also received some consideration in the treatment of dysmenorrhea for similar reasons. Vitamin B complex has been employed based on the assumption that the dysmenorrheic symptom complex is caused by a high blood estrogen level. Estrogens are metabolized in the liver and the vitamin B complex facilitates this function of the liver. Massive doses of vitamin C have been used because of its effect upon capillary permeability. A deficiency of vitamin C has been incriminated as a possible factor in increasing capillary permeability, thus producing edema in the endometrium and an unusually large tissue mass for the uterus to excrete.

From what has been said regarding therapy in dysmenorrhea, it is obvious that no one regimen of therapy is suitable for all cases. Success can be best achieved by the careful study of the individual characteristics of the patient. The problem involves not only the endocrine system of the patient but also her psychic pattern.

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# PART VIII

## EFFECT OF PHARMACOLOGIC AGENTS ON METABOLISM

## 51

## *The Response of Water Balance to Pharmacologic Agents*

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The maintenance of the water balance of an organism is of prime importance for its physiologic well-being. Shifting of the water balance occurs in many diseases. In certain pathologic states one of the outstanding objective symptoms is the infiltration of fluid into the tissues or edema. In the section on circulation it was pointed out that in congestive heart failure the circulatory embarrassment resulted in anasarca and ascites. In hydremic nephritis the inability of the kidney to excrete saline substances results in water retention and edema. In diseases of the adrenal cortex the capacity of the kidney to retain an adequate sodium content of the tissues is impaired. With the loss of sodium in the urine an inordinate amount of fluid is also lost. The body becomes dehydrated, and one of the symptoms of the disease is hemoconcentration and generalized dehydration.

Because pharmacologic agents are capable of evoking a favorable shift in water balance when it is altered in some diseases, drugs of this class are of great clinical importance.

**Body water.** Water is the most abundant of all chemical compounds in the human body. It constitutes approximately ⅔ of the entire body weight. Water is the fluid in which the chemical reactions which constitute life occur. Its importance is emphasized by the fact that if 20 to 25 per cent of the body water is lost, death usually results.

The more readily available a substance is, the more prone one is to take it for granted. This is true for water. It is of interest to review certain of the physical and chemical properties of the fluid which are so ideally appropriate to it as the "milieu of life." It is an excellent solvent for inorganic salts. Water permits many organic substances to be dispersed through it in the colloidal state. There exists a vast range of temperature between its boiling and freezing points. The dielectric constant of water is high, and thus in it ionization of electrolytes occurs to a maximal degree. This facilitates interaction at a low temperature. In addition, water is an excellent lubricant between membranes, and it also functions well as a heat insulator. Many other properties of water of physiologic importance could be cited. These, however, are sufficient to arouse one's interest again in this most remarkable liquid.

**Normal water balance.** The water balance of the body is maintained against a continual water intake and a continuous water excretion. The intake of water occurs mainly in 3 ways:

1. Through fluids present in the diet
2. Through solids in the diet which are greatly hydrated
3. Through the oxidation of hydrogen in foodstuffs in tissues

There are 5 principal avenues by which the continuous excretion of water occurs:

1. Through the kidneys as urine
2. Through the skin as sweat
3. Through the lungs as vapor
4. Through the intestinal tract as feces
5. Through the excretion of tears and saliva

The loss of water in urine constitutes from about 50 to 60 per cent of the total excretion. Together, the other channels remove approximately ½ of the body water loss.

In health, the water intake and excretion are

approximately the same when measured over short periods of time. When determined over long periods of time for a person in "water equilibrium," the agreement is remarkably close. Within the body, water is constantly undergoing shifts to meet the physiologic demands of the organism. Water composes from ½ to ¾ of the body weight of a normal person. The water content of the body is inversely proportional to the amount of adipose tissue. The water is distributed in the following manner: (1) interstitial water, 16 to 18 per cent; (2) intracellular water, 30 to 40 per cent; (3) plasma water, 4.5 per cent; and (4) transcellular water, 1 to 3 per cent of body weight.

**Maintenance of water balance.** One of the principal factors in the maintenance of water balance among the compartments is the osmotic pressure of electrolytes and the selective ion permeability of cellular membranes. The plasma proteins play an important role in the maintenance of blood volume and hence in determining the water content of tissues. The plasma proteins cannot diffuse through the capillary wall because of their large particle size. Thus they act as a force in holding water in the blood through the osmotic pressure which they exert.

Extracellular fluid contains sodium chloride in isotonic concentrations. Hence the ingestion of 9 gm. of sodium chloride will necessitate the holding in the interstitial fluid of 1 L. of water to maintain the normal osmotic balance. Conversely, the loss of sodium chloride such as occurs in Addison's disease will require the loss of water to compensate for the diminished osmotic pressure. Indeed, salts containing potassium and sodium ions are employed as pharmacologic agents to effect a favorable shift of water balance in disease.

As has been stated previously, the kidney plays the dominant role in water excretion and hence in the maintenance of water balance. Let us therefore first give consideration to those drugs which act upon the kidney, increasing the flow of urine. These drugs are called *diuretics*.

### THE KIDNEYS AND WATER BALANCE

**Functions of the kidney.** A review of the functional activity of the kidney will shed light upon the selection of the various agents used as diuretics. Essentially the kidney enjoys a 5-fold function as follows:

1. To excrete the end products of nitrogenous metabolism.
2. To excrete inorganic salts not needed by the tissues.
3. To maintain the osmotic pressure of the blood and tissues.
4. To maintain the acid/base equilibrium of the blood.
5. To elaborate a principle (renin) concerned with arterial tension.

The nitrogenous wastes of the body such as urea are secreted in solution in the urine. Substances of this character serve to increase urine flow. When ingested, urea is absorbed from the gastrointestinal tract and circulates in inordinately high concentrations in the blood; it is removed from the blood by the kidney and excreted in the urine in dilute solution. Hence water is excreted, and urea serves as a diuretic drug.

The second function of the kidney, namely, the removal of excessive quantities of inorganic salts, also serves as a principle for the selection of diuretic drugs. Various ions enjoy different renal thresholds. For example, the sodium ion has a high renal threshold, and the kidney will permit 142 mEq./L. of sodium ion to circulate in the blood. On the other hand, the potassium ion concentration of the plasma is low, about 4 mEq./L. Potassium salts therefore are removed from the blood. The kidney possesses the capacity of concentrating potassium 50-fold from the blood to the urine. Therefore potassium salts cause water excretion and serve as diuretics.

In the maintenance of the osmotic pressure of the blood and tissues, the kidney is called upon to secrete excessive quantities of fluid or salts, depending upon the osmotic shift. Indeed, plasma water remains remarkably constant and does not show alteration until the water content of the interstitial fluid has been changed by approximately 20 per cent. Accordingly water serves as a diuretic. If one ingests 2 to 3 L. of water during the course of 1 hour, approximately the same volume will be voided within a period of 5 hours. Water is a natural physiologic diuretic.

It appears that the hypothalamus contains definite receptor centers that are sensitive to osmotic pressure changes in the extracellular fluid. These have been called *osmoreceptors*. The regulatory mechanism is mediated through the antidiuretic hormone (ADH). When large volumes of water are ingested, ADH circulating in the blood is diminished, and tubule reabsorption is reduced. Diuresis results. The secretion of water above that required for the solutes of the urine is conditioned by and dependent upon a fall in the concentration in blood and kidney of ADH. The secretion of this hormone is controlled, through the nervous system, by the concentration of water in blood and tissues.

The kidney plays an important part in the maintenance of the acid/base equilibrium of the blood. The lungs excrete the anhydride of carbonic acid, carbon dioxide. The kidney excretes fixed acid. The kidneys excrete daily an amount of fixed acid, such as phosphoric and uric, equivalent to from 20 to 50 ml. of normal sodium hydroxide. The kidneys will excrete additional quantities of acid if a substance is ingested which tends to shift the $H_2CO_3$:$BHCO_3$ ratio of the blood to the acid side. Ammonium and calcium chlorides are compounds of this character. Their diuretic action depends upon the fact that their ingestion induces incipient acidosis. To combat this, more acid is excreted in the urine, this is diluted with water, and hence diuresis is effected. Likewise, the ingestion of alkaline salts such as sodium bicarbonate produces diuresis. However, these are not so effective as the acidotic agents.

The fifth function of the kidney, listed previously, is hormonal in character and not directly associated with the function of diuretic drugs.

**The formation of urine.** Three discrete processes are involved in the formation of urine. These are: (1) glomerular ultrafiltration, (2) tubular reabsorption, and (3) tubular secretion. The glomerular filtration membranes are large, covering an area of several square meters. It is estimated that approximately 150 L. of blood pass through the human kidneys in a period of 24 hours. From this large volume of glomerular filtrate about 1 per cent, or 1.5 L., of urine is formed. The noncolloidal constituents of the plasma pass through the glomerular filtration bed.

The colloidal constituents of the plasma do not pass through the glomerulus. As the glomerular filtrate proceeds through the tubules, only those substances which are necessary to the plasma and tissues are reabsorbed. Among these substances are water, glucose, salts, amino acids, and bicarbonate. These compounds which are reabsorbed are called *threshold substances*. Other compounds in the glomerular filtrate which are not materially reabsorbed are designated as *low* or even *nonthreshold* substances. Sulfate, phosphate, urea, and creatinine are such substances. The filtration glomerular pressure involves the following factors. The driving force is the arterial blood pressure, which is equal to about 75 mm. Hg. This is opposed by the osmotic pressure of the colloidal constituents of the plasma. This pressure is equal to about 25 mm. Hg. Therefore the effective glomerular filtration pressure is essentially the difference between the arterial pressure and the osmotic pressure of the plasma proteins. There are other factors involved, such as the pressure of the interstitial fluid and the force of about 10 mm. Hg required to move the filtrate through the tubules. It is evident that blood pressure plays an important part in glomerular filtration. If in laboratory animals the arterial tension is reduced to ⅓ its normal value, as a rule glomerular filtration ceases. Conversely, drugs which elevate the blood pressure often increase the flow of urine.

The glomerular filtration rate in an adult is about 115 ml./minute. About 99 per cent of the fluid is returned to the blood, producing 1 ml. of urine. Thus it is obvious that to change the quantity of urine excreted the rate of tubule reabsorption can be more readily altered than the larger volume of glomerular filtrate. Changing the quantity of tubule reabsorption from 99 to 98 ml. per minute doubles the urinary output.

The kidneys are stationary organs, not engaged in muscular movement like the heart and skeletal muscle, yet the amount of work which they perform is stupendous. It is osmotic work. Approximately 11 per cent of the oxygen consumption of the entire body is used by the kidneys. The heart uses 0.054 ml. $O_2$/gm./min. The kidneys require 0.05 ml. (Barcroft and Brodie, 1905).

The tubules perform much of their osmotic work in the loop of Henle. The depression of the freezing point of blood is 0.56°C. The kidney may concentrate the salts in a filtrate from blood and excrete a urine with a freezing point depression of 3.2°C. It is estimated that in concentrating a liter of fluid from $\Delta$ 0.56°C to the freezing point of normal urine the osmotic work is equal to 500 kg. meters or 3500 foot pounds (Cushny, 1926). Substances which increase the osmotic pressure of the glomerular filtrate diminish water reabsorption by the tubules and produce diuresis. Clinically, advantage is taken of this fact, and substances such as glucose, sucrose, and mannitol are injected intravenously to produce diuresis.

**Measurement of kidney function.** Routinely in clinical medicine the functional activity of the kidney is measured for diagnostic purposes. As a first approximation of the kidney function, the capacity of the organ to excrete a dye injected into the blood has been used for 5 decades. The dye *phenolsulfonphthalein* is most extensively employed.

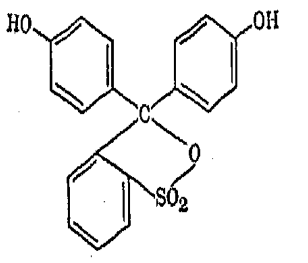
The normal excretion of phenolsulfonphthalein is 25 to 45 per cent within the first 15 minutes after an intravenous injection. From 50 to 65 per cent of the dye is normally excreted during the first hour and from 65 to 85 per cent within 2 hours. Following the intramuscular injection of the dye, from 40 to 50 per cent is eliminated in the first hour and from 60 to 75 per cent at the end of a 2-hour period.

The procedure frequently used is as follows: the patient is given from 200 to 400 ml. of water to drink to ensure a liberal excretion of urine. Exactly 1 ml. of the monosodium salt of phenolsulfonphthalein solution (1 ml. = 6 mg.) is injected either into the lumbar muscles or into one of the antecubital veins. When the injection is made intramuscularly, the patient is instructed to empty the bladder completely at the end of 70 minutes. The patient is told to void again into a second container at the end of 120 minutes. When the injection is made intravenously, urine samples are collected at 15, 60, and 120 minutes after the injection.

The separate urine specimens are made alkaline with 25 per cent sodium hydroxide solution and diluted to 1000 ml. They are then compared with a standard phenolsulfonphthalein solution containing 6 mg. ≎ 100 per cent elimination. The comparison is made colorimetrically.

The test is readily carried out and the equipment required is simple. Its clinical utility is evidenced by the widespread use of the test. The principal criticism of the test is its lack of sensitivity. It must be looked upon as a first approximation of kidney function. Gross damage to the excretory function of the kidney is readily detected. Incipient renal insufficiency is frequently not made manifest by the so-called PSP test.

Phenolsulfonphthalein and the sterile solution for injection are official in the Pharmacopeia. The dye is also called *phenol red*. The chemical constitution of phenolsulfonphthalein may be observed in the accompanying formula.



Phenolsulfonphthalein, U.S.P.

**Kidney clearance tests.** Certain substances in the blood pass through the glomerular membrane and are not reabsorbed at all by the tubules. Creatinine is such a substance. Other substances injected into the blood pass completely into the glomerular filtrate but are rejected entirely by the tubules. Compounds of this character enable one to measure the *kidney clearance*. In addition, knowledge of the kidney clearance test has shed much light on the efficiency and mechanism of action of many diuretic drugs.

Inulin, a polysaccharide found in Jerusalem artichokes and other plants, has been used extensively by H. W. Smith and associates (1938 *et seq.*) for the measurement of glomerular filtration. The maximal absorptive function of the tubule cells can be shown by glucose absorption (glucose Tm). The maximal excretory function of the tubules can be determined by Diodrast (iodopyracet, Diodrast Tm) (see page 796). The amount of plasma flowing through the kidneys in a unit time can be demonstrated by Diodrast (Diodrast clearance).

The measurement of inulin clearance by the kidney is a determination of glomerular filtration rate. Using this test, the likely site of action of the xanthine diuretics such as caffeine and theobromine has been demonstrated. When these diuretics are administered to individuals in whom inulin has been injected intravenously, the total quantity of inulin in the urine is not altered. However, the volume of urine is increased. Therefore the concentration of inulin in the urine is diminished. As inulin excretion is a measure of glomerular filtration rate, it appears that the diuretic does not act upon the glomeruli, increasing filtration speed. On the other hand, the site of action indicated is the tubule reabsorption mechanism. One concludes therefore that the mechanism of the diuretic action of these drugs is in the diminution of the volume of water reabsorbed by the tubular epithelium.

### VISUALIZATION OF URINARY TRACT

The intravenous injection of soluble organic compounds containing iodine makes it possible to produce satisfactory roentgenograms of the urinary tract. Many such compounds are now available, sufficiently devoid of untoward side actions to be useful for this purpose. These compounds may be used also for ureteral retrograde pyelography. The following table lists these agents which are official.

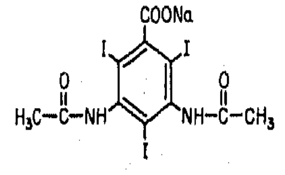
### OFFICIAL RADIOPAQUE UROGRAPHIC AGENTS

Methylglucamine Diatrizoate Injection, U.S.P. (Renografin)
Methylglucamine Iodipamide Injection, U.S.P. (Cholografin)
Sodium Acetrizoate Injection, U.S.P. (Urokon)
Sodium Diatrizoate Injection, U.S.P. (Hypaque)
Sodium Diprotrizoate Injection, U.S.P. (Miokon)
Iodipamide Sodium Injection, N.F. (Cholografin)
Iodopyracet Injection, N.F. (Diodrast)
Methiodal Sodium Injection, N.F. (Skiodan)
Sodium Iodomethamate Injection, N.F. (Neo-Iopax)

There are also numerous nonofficial radiopaque urographic agents. Among the newer drugs of this class is *Meglumine iothalamate*, known as *Conray*. It is a sterile solution of 60 per cent W/V of the N-methylglucamine salt of 5-acetamido, 2,4,6-triido-N-methylisophthalamic acid. Its use is similar to that of the official agents of this class.

**Sodium Diatrizoate Injection, U.S.P. (Hypaque).** Sodium diatrizoate injection is a 50 per cent solution of sodium diatrizoate. This agent typifies the class of radiopaque urographic agents and enjoys extensive use. Its use therefore will be discussed as a prototype of the other agents in this class of drugs.

The chemical composition of sodium diatrizoate is shown in the formula:



Sodium Diatrizoate, U.S.P.
Hypaque
(sodium 3,5-diacetamido-2,4,6-triiodobenzoate)

Sodium diatrizoate is a white, crystalline powder which is readily soluble in water, yielding a 50 per cent solution with a pH range of 7.0 to 8.5.

*Diagnostic use.* When sodium diatrizoate injection is administered intravenously, it is carried to the kidneys with great rapidity and excreted in the urine unchanged. With normal renal function, excretion begins immediately after injection and suitable roentgenograms can be obtained within 5 minutes after injection.

All of these iodine-bearing organic compounds should be used with caution. Mild reactions to the injection of these agents are not uncommon. Flushing of the skin, sensations of warmth, nausea, and vomiting may be encountered. Skin rash and respiratory distress have occurred infrequently. The persistence of the untoward effects is seldom longer than 1 hour. A sudden fall in blood pressure may accompany the injection of these agents. In some instances it may be sufficiently pronounced that cyanosis, dyspnea, and unconsciousness may ensue. These agents are interdicted in patients with severe liver disease, advanced renal impairment, uremia, active tuberculosis, hyperthyroidism, or marked debility.

Sobin *et al.* (1959) studied the nature of the adverse reactions to radiopaque agents. They observed the effect of the injection of these agents on the small blood vessels at the corneal-scleral junction in man and rabbits. In 20 of 24 patients studied, changes in the vessels were induced by the injection. The changes were seen 1 to 2 minutes after the injection. Microcirculation was retarded. They state: "The fine granular appearance of the erythrocyte column was quickly replaced by a much coarser granularity with red blood cell masses and clear irregular intravascular plasma zones between the red blood cell masses." Actual stasis did not occur, but vasoconstriction was noted in both minute arterial and venous vessels. There was an over-all decreased vascularity in the microscopic field. This alteration of circulation reached a peak in 4 to 6 minutes after injection and was usually normal again in 20 minutes. These interesting studies are thought provocative and are perhaps indicative of the mechanism of some of the adverse reactions to radiopaque agents.

It appears that sodium diatrizoate evokes a minimal incidence of adverse side effects. The administration of sodium diatrizoate is carried out as follows. One milliliter of the injection is given intravenously as a test dose for the patient's sensitivity. After the appropriate preparation of the patient the evening before and examination of a film taken immediately before injection to rule out confusing gas shadows, the injection is given. Usually 30 ml. of the 50 per cent solution is injected intravenously in 1 to 3 minutes. Exposures for visualization are then made 5, 10, or 15 minutes after the injection.

Sodium diatrizoate, like many of the radiopaque agents, is used in cinocardioangiograms. For this purpose solutions as concentrated as 90 per cent are employed. The solution is administered by catheter at selected cardiac locations (0.5 to 0.7 ml./kg.). It has been found that sodium diatrizoate causes fewer adverse systemic reactions than other radiopaque agents used for this purpose.

### DIURETICS

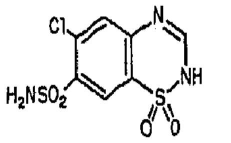
In the therapeutic use of diuretic drugs one of the most important points to bear in mind is that their action is dependent upon functionally active kidneys. In edema associated with hydremic nephritis the kidneys are impaired, and the use of diuretic drugs may be interpreted as an attempt to force an organ with advanced sclerosis to perform more work under the stimulus of the drug. In such conditions the diuretic is generally of little value and may actually do harm. In edema associated with congestive heart failure, however, the diuretic drugs may be very helpful. In conditions of this kind, in which the retention of water is not directly associated with impaired kidney function, the diuretics find their principal field of usefulness.

A variety of chemical compounds of diverse chemical structure act upon the kidneys and reduce the tubular reabsorption of electrolytes and water. The xanthine alkaloids such as theobromine exhibit a mild diuretic action. Organic mercury compounds evoke diuresis, and until comparatively recently these agents were the drugs of choice in the treatment of edema of cardiac origin. The use of acetazolamide (Diamox) as a diuretic, which owes its activity to its capacity to inhibit carbonic anhydrase in the kidney, initiated the investigation of other compounds which might cause diuresis by this mechanism. These researches were rewarded by the discovery of a type of chemical structure new to drug therapy, namely, chlorothiazide. Although chlorothiazide is not a potent carbonic anhydrase inhibitor, it evokes a diuretic action tantamount to that produced by the organic mercurials. Within a decade this compound and its derivatives have come to occupy a position of preeminence in this category of drugs and in large measure have replaced the organic mercurials as diuretics.

**Chlorothiazide and derivatives.**

Chlorothiazide is the first diuretic drug devoid of an atom of mercury in the molecule which could adequately compete with the organic mercurials as a potent and dependable diuretic agent.

**Chlorothiazide, U.S.P. (Diuril).** Chlorothiazide is a specific diuretic agent which markedly increases the excretion of sodium and chlorine ions and water by the kidneys. Its chemical structure is shown in the formula:



Chlorothiazide, U.S.P.
Diuril
(6-chloro-7-sulfamyl-2 H-1,2,4-benzothiadiazine-1,1-dioxide)

Chlorothiazide occurs as a white, crystalline powder which is sparingly soluble in water.

*Pharmacologic response to chlorothiazide.* The principal pharmacologic response to chlorothiazide is upon renal function. Here, as previously stated, it increases the excretion of the ions of sodium and chlorine and secondarily increases the excretion of water. The renotropic action of chlorothiazide is manifested in its capacity to inhibit the tubule reabsorption of electrolytes, mainly $Na^+$ and $Cl^-$. To a lesser degree it affects the reabsorption of $K^+$ and $HCO_3^-$. This is illustrated in the experiments of Beyer (1958) on the renal clearance of electrolytes in dogs upon the administration of chlorothiazide. Chlorothiazide evoked a 35-fold increase in $Na^+$ excretion, a 26-fold increase in $Cl^-$ elimination, and a 3.8-fold increase in $K^+$ excretion. The urinary pH increased from about 6 to 8, which was interpreted as the result of a net increase of $HCO_3^-$ excretion. During these studies there was no significant change in the glomerular filtration rate. Further studies demonstrated that following the administration of large quantities of sodium chloride, chlorothiazide evoked a substantial increase in the renal excretion of $Na^+$ and $Cl^-$ and had a limited effect upon $K^+$, $HCO_3^-$ excretion and urinary pH. The saluretic and diuretic action of chlorothiazide was effective in acidotic and alkalotic states.

Chlorothiazide is excreted unchanged in the urine. In a period of 6 hours, 95 per cent of the chlorothiazide injected intravenously was ex-

KARL H. BEYER, JR.

*Leading American pharmacologist in the field of chlorothiazide diuretics*

"At the risk of erring in detail and concept, we have attempted to consider . . . how the physiological disposition of drugs, particularly chlorothiazide and its congeners, influences their effect on salt and water elimination."

creted in the urine. During its sojourn in the body chlorothiazide is distributed in the extracellular fluid. The simultaneous administration of probenecid reduces the renal tubular excretion of chlorothiazide without reducing its capacity to inhibit the reabsorption of Na$^+$ and Cl$^-$. This is indicative of the fact that the mechanism of tubular elimination of chlorothiazide must be similar, in general, to that which is responsible for the secretion of *p*-aminohippuric acid, phenol red, and penicillin G (see page 91). The renal excretion of these agents represents competitive inhibition of common substrates for active transport system. The clearance of chlorothiazide is depressed by probenecid, which competitively inhibits the tubular secretion of *p*-aminohippuric acid.

*Mechanism of action.* Chlorothiazide evokes the urinary excretion of Na$^+$, Cl$^-$, K$^+$ and water, similar to a mercurial diuretic. The latter, however, does not increase the urinary pH as does chlorothiazide. The increase of the urinary pH produced by chlorothiazide is also evoked by diuresis with acetazolamide, a potent carbonic anhydrase inhibitor. Acetazolamide, however, does not elicit an appreciable chloruresis, as does chlorothiazide.

Furthermore, the diuretic action of the mercurial diuretics is almost nullified by alkalotic states and enhanced by acidosis. Neither state exhibits any appreciable effect upon the action of chlorothiazide. Acetazolamide diuresis is incompatible with the acidosis produced by ammonium chloride. Chlorothiazide diuresis is not affected.

Chlorothiazide was shown by Beyer (1958) not to act as a true antagonist to aldosterone or the posterior pituitary antidiuretic hormone.

Implicit in these statements is the fact that the mechanism of the diuretic action of chlorothiazide does not fit into any of the established patterns of diuretic action assigned to the classical diuretics. Beyer (1958) proposed that the site of the critical saluretic action of chlorothiazide was the proximal convoluted tubules. This proposal appears to remain unchanged. The agent depresses the proximal reabsorption of sodium, resulting in an iso-osmotic reduction in water reabsorption at that site. Chlorothiazide and its congeners are transferred from the cells across the luminal border of the proximal segment of the nephron. This has been demonstrated from clearance data and also by "stop-flow" experiments in dogs, designed to locate the site of tubular secretion.

The precise mechanism of the diuretic effect has not been clearly delineated. There appears to be no correlation between the diuretic action of these agents and their capacity to inhibit carbonic anhydrase *in vitro*. In addition, the secretion of the thiazides by the proximal tubules does not correlate well with their carbonic anhydrase inhibitory activity or their saluretic potency. Correlation between chemical constitution and diuretic action has not revealed a clue to the renotropic effect, since such a wide variety of chemical structures among the thiazides appear to exert the same qualitative effect.

There still remains the possibility, suggested by Beyer (1958), that the thiazides, showing comparatively weak inhibitory action of carbonic anhydrase *in vitro*, may be secreted in the proximal portion of the tubule and not concentrated in the erythrocytes. Such a compound would evoke a copious excretion of Na$^+$ and Cl$^-$ and to a lesser extent the excretion of HCO$_3^-$. The excretion of HCO$_3^-$ and K$^+$ may be indicative of their inhibition of carbonic anhydrase. There remains, however, the possibility that chlorothiazide and its congeners may function as diuretics by an additional mechanism which as yet remains undisclosed.

*Clinical use.* Chlorothiazide has been used successfully in a variety of clinical conditions where salt retention is a factor in the clinical course of the disease. The principal use of chlorothiazide is in the treatment of *edema in congestive heart failure.* Other uses are in the treatment of premenstrual tension, edema and toxemia of pregnancy, hypertension, edema associated with hepatic disease, and renal edema. Before the discovery of chlorothiazide the organic mercurials were the only diuretic agents of sufficient potency and dependability to warrant general use in the treatment of edema of cardiac origin. Ford *et al.* (1958) compared a number of the available diuretics in congestive heart failure and found that chlorothiazide was equipotent with the organic mercurial meralluride. The latter drug was administered intramuscularly and chlorothiazide was administered orally. It is clear that chlorothiazide offers an advantage for repetitious use in this condition. The findings of Ford have been confirmed by numerous investigators. For example, Warshaw (1959) found chlorothiazide effective as a diuretic in 85 of 97 cases of congestive heart failure. He encountered certain cases where the drug was ineffective and others in whom tolerance developed. In these cases recourse to parenteral mercurial diuretics was necessary.

Oral doses of 0.5 to 1 gm. daily of chlorothiazide appear to be comparable in diuretic potency to the oral administration of mercurial diuretics: 1 to 2 gm. daily of chlorothiazide evokes a degree of diuresis comparable to the parenteral use of the mercurial diuretics. The onset of action of chlorothiazide is about 2 hours, reaching a peak in 4 hours and persisting for 6 to 12 hours. For patients in whom the oral route is not available, chlorothiazide, "Lyovac Diuril," is available for intravenous use; 0.5 gm. of the sodium salt is dissolved in 18 ml. of "water for injection." The solution is alkaline and extravasation should be carefully avoided.

*Cautions in therapy.* Chlorothiazide is a potent drug affecting the electrolyte and water balance of the patient, and therefore it must be administered under careful medical supervision. Nausea, vomiting, diarrhea, dizziness, and paresthesias have been occasionally encountered as side effects with chlorothiazide therapy. Skin rash has been rarely reported. Blood dyscrasias resulting from its use have not come to our attention.

The most frequent adverse sequela of chlorothiazide therapy is electrolyte imbalance; frequent checks on the plasma electrolyte levels are desirable. If the excretion of Cl$^-$ exceeds that of Na$^+$, *hypochloremic alkalosis* may result. One major problem is that of *hypokalemia.* Although Na$^+$ is the principal cation excreted with chlorothiazide therapy, with a marked diuresis much K$^+$ may also be excreted, giving rise to hypokalemia. A liberal intake of fruit juices and/or the administration of potassium chloride is advised as a prophylactic measure. The loss of potassium may be especially dangerous to the digitalized patient. Hypokalemia may render the usual maintenance therapeutic dose of digitalis toxic to the patient with congestive heart failure.

Nitrogen retention has been encountered infrequently; no adequate explanation has been offered to account for this side effect.

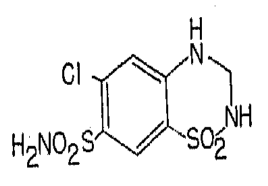
When chlorothiazide is used in renal or hepatic edema, azotemia may develop. If it becomes progressive, the therapy with chlorothiazide should be discontinued. Elevation of the uric acid serum level has precipitated attacks of gout in susceptible individuals.

There has been some evidence that chlorothiazide diminishes glucose tolerance; therefore, in diabetes it must be used with caution.

Thrombocytopenia, leukopenia, and agranulocytosis have been encountered with chlorothiazide therapy. Fortunately, their occurrence is rare. The use of chlorothiazide in the treatment of hypertension is discussed on page 691. There appears to be no doubt that the discovery of this drug represents a major development in the field of diuretic therapy. It is of great interest to note that within a period of a year after the discovery and clinical use of chlorothiazide the synthesis of a strikingly similar chemical structure, namely, hydrochlorothiazide, resulted in the availability of a diuretic with about 10 times the potency of chlorothiazide. Indicative of the specific or renotropic action of chlorothiazide and hydrochlorothiazide is the fact that although hydrochlorothiazide is at least 10 times more potent than chlorothiazide, the estimated LD$_{50}$ of chlorothiazide is 200 mg./kg. and that of hydrochlorothiazide is greater than 350 mg./kg.

The development of hydrochlorothiazide was followed by the synthesis and clinical use of other thiazides having 100 (trichlormethiazide) to 1000 (cyclopenthiazide) times the natriuretic activity of chlorothiazide (Beyer and Baer, 1961).

**Hydrochlorothiazide (Esidrix, Hydrodiuril).** Hydrochlorothiazide chemically represents the molecule of chlorothiazide in which the double bond in the heterocyclic ring between the nitrogen and carbon atom has been removed by hydrogenation, as shown in the formula:



Hydrochlorothiazide
(6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide)

Hydrochlorothiazide occurs in a white, crystalline powder which is very slightly soluble in water.

*Pharmacologic response.* As has been stated, the principal response to the administration of hydrochlorothiazide to man and laboratory animals is that of saluresis and diuresis. The mechanism of action which has been discussed under chlorothiazide applies to hydrochlorothiazide, with certain minor differences which appear to be significant. It has been stated that hydrochlorothiazide is at least 10 times more potent as a diuretic than chlorothiazide. Beyer (1958) postulated that chlorothiazide probably evoked diuresis by its conformity to the group of carbonic anhydrase inhibitors, providing a high concentration in the proximal portion of the nephron, but not in the erythrocytes. *In vitro* studies show hydrochlorothiazide to be only ⅙ as potent as chlorothiazide as a carbonic anhydrase inhibitor. Either hydrochlorothiazide must enjoy a far greater specificity for renal carbonic anhydrase than does chlorothiazide, or the mechanism of diuretic action is achieved by a mechanism which is not yet known. It appears that the latter is likely the case.

Sheppard *et al.* (1960) used tritium-labeled hydrochlorothiazide to study the distribution, fate and excretion of the drug in rats. The agent is rapidly absorbed and 43 to 69 per cent is excreted in the urine within 48 hours. There was no evidence of metabolic alteration.

*Clinical use.* Hydrochlorothiazide enjoys the same type of clinical application as chlorothiazide. Owing to its greater potency it appears to be the drug of choice between the 2 diuretics. The smaller dosage tablet of 25 mg. of hydrochlorothiazide instead of 250 mg. of chlorothiazide provides for a more convenient form of medication when other agents, such as reserpine, are administered simultaneously in the same dosage form. The average dose of hydrochlorothiazide is 75 mg., 3 tablets daily. After a week of therapy the dose may be adjusted upward or downward to meet the needs of the patient. The same precautions discussed under therapy with chlorothiazide prevail with the administration of hydrochlorothiazide. It does appear, however, that hydrochlorothiazide offers a greater flexibility of dosage and fewer untoward side effects than therapy with chlorothiazide.

**Other thiazide diuretics.** It has been demonstrated that many derivatives of the thiazide molecule are capable of serving as excellent diuretic drugs. Certain modifications of the molecule diminish diuretic activity, while other

TABLE 51-1

*Thiazide Diuretics**

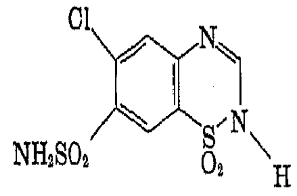
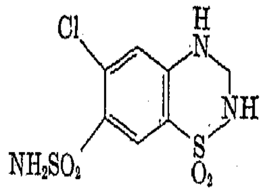
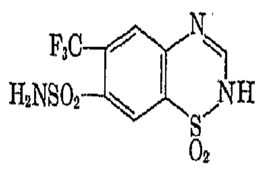
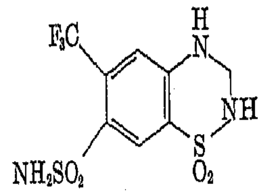
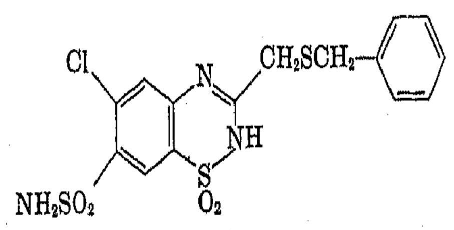
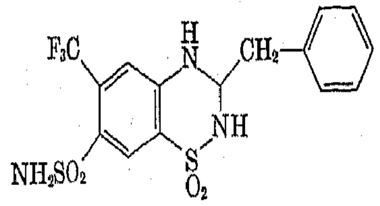
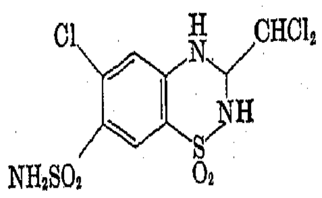
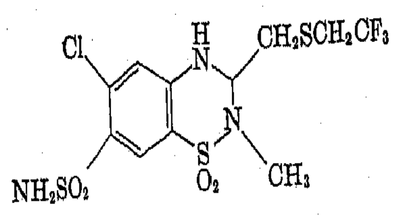
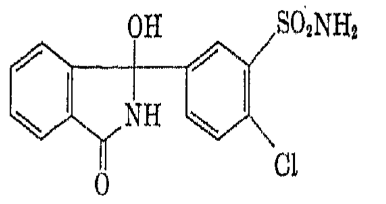
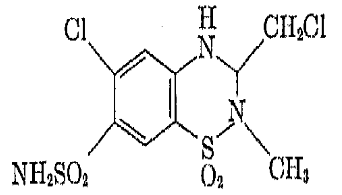
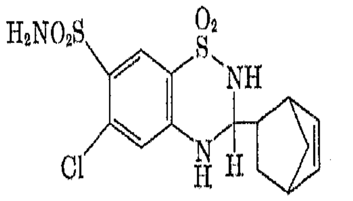
| Generic Name | Trade Name | Structure | Dose | Na Excretion† | Na/K Ratio Excretion |
|---|---|---|---|---|---|
| | | | *mg.* | *mEq./24 hr.* | |
| Chlorothiazide | Diuril |  | 1000<br>2000 | 44<br>104 | 2.5 |
| Hydrochlorothiazide | Esidrix |  | 25<br>50 | 90<br>150 | 2.9 |
| Flumethiazide | Ademol |  | 1000<br>2000 | 40<br>90 | 3.9 |
| Hydroflumethiazide | Saluron |  | 25<br>50 | 85<br>133 | 3.4 |
| Benzthiazide | Exna |  | 25<br>50 | 80<br>130 | 4.8 |
| Bendroflumethiazide | Naturetin |  | 2.5<br>5.0 | 110<br>170 | 8.1 |
| Trichlormethiazide | Naqua, Metahydrin |  | 4.0<br>8.0 | 106<br>168 | 6.0 |
| Polythiazide | Renese |  | 4.0<br>8.0 | 136<br>194 | 8.4 |

TABLE 51-1—*Continued*

| Generic Name | Trade Name | Structure | Dose | Na Excretion‡ | Na/K Ratio Excretion |
|---|---|---|---|---|---|
| | | | *mg.* | *mEq./24 hr.* | |
| Chlorthalidone‡ | Hygroton |  | 25<br>50 | 112<br>164 | 18.2 |
| Methyclothiazide | Enduron |  | 5.0<br>10 | 15.8<br>236 | 3.8 |
| Cyclothiazide | Anhydron |  | 2 | 249 | 2.4 |

* Excretion data from Ford, 1961.

† Increases in excretion over control values.

‡ Phthalimidine derivative.

changes markedly enhance the diuretic potency. The newer thiazides have a more potent and more enduring natriuretic activity. In addition, the excretion of potassium has been markedly reduced with some of the newer derivatives. One of the agents, chlorphthalidone, differs from the thiazides in that it contains a phthalimidine nucleus.

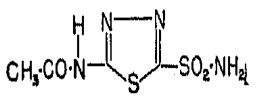
The chemical structures, dosage, and comparative activity of these diuretics are shown in table 51-1.

**Choice of a thiazide diuretic.** The data in table 51-1 reveal that strides have been made by molecule manipulation among the thiazide diuretics. The advances are mainly in potency, duration of action, and diminution in potassium excretion. It is clear that polythiazide, trichlormethiazide, and bendroflumethiazide of the thiazides and chlorphthalidone are the most potent diuretics. Their duration of action extends over 24 hours, and they provoke the least potassium loss. Nevertheless it appears that the first of the series, chlorothiazide, and its companion drug hydrochlorothiazide are the most extensively used and the data on their side effects and mechanism of action are more complete than with any of the newer agents. Familiarity with the use of a drug on the part of the physician is a salient factor in its continued use, despite slight advantages that appear to be inherent in the use of newer drugs of a similar character.

The most common untoward effect of these drugs is acute or chronic hypokalemia. This is readily avoided by measures that have previously been discussed. Although the drugs have no manifest inherent toxicity, as the newer agents are more generally used it is likely that cases of severe toxicity might occur. Thus with the new phthalimidine derivative chlorthalidone, Klein (1963) reported a case of agranulocytosis believed to be induced by therapy with this agent. The authors hold the view that unless the patient is most carefully controlled and under constant vigilance for the occurrence of serious side effects, the drugs of choice for the ambulatory patient are chlorothiazide and hydrochlorothiazide. These 2 drugs constitute more than 50 per cent of all of the thiazide diuretic therapy.

### Diuresis and carbonic anhydrase.

Carbonic anhydrase is an enzyme which converts carbon dioxide entering the blood from the tissues into carbonic acid. It was established many years ago that the administration of sulfanilamide caused the inhibition of carbonic anhydrase. The inhibition of carbonic anhydrase resulted in diuresis. Thus, investigators sought to prepare a potent carbonic anhydrase inhibitor with a low degree of toxicity. Roblin and Clapp (1950) prepared a series of heterocyclic sulfonamides; among these, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, as shown in the formula, appeared to meet these requirements.



Acetazolamide, U.S.P.
Diamox

Acetazolamide is a white, crystalline compound which is slightly soluble in water.

**Mechanism of action of acetazolamide.** Acetazolamide is different in chemical constitution and pharmacologic activity from the generally employed bacteriostatic sulfonamides. It is rapidly absorbed from the gastrointestinal tract and almost completely excreted unchanged in the urine within 24 hours. Acetazolamide is a remarkably nontoxic agent when administered in large dosage schedules to the usual laboratory animals. Blood plasma levels are maintained for 6 to 12 hours after its administration. The renal excretion rate appears to be about ½ its glomerular filtration rate. The drug is distributed in the erythrocytes and other tissues but mainly in the kidney.

Pitts and Alexander (1945) showed that acidotic dogs given adequate amounts of phosphate buffers excreted more $H^+$ in the urine than was present in the glomerular filtrate. They postulated that the urine was acidified by the secretion of $H^+$ by the tubule cells, which involved the exchange of $Na^+$ for $H^+$. Further, they postulated that $H_2CO_3$ was the source of $H^+$. They showed that agents such as sulfanilamide and acetazolamide, which prevented the reaction $CO_2 + H_2O \rightarrow H_2CO_3$ by inactivating carbonic anhydrase, impeded the acidification process of the urine.

Three important renal mechanisms for the maintenance of the extracellular $HCO_3^-$ level are (1) the reabsorption of $HCO_3^-$, (2) the acidification of urinary buffers, and (3) the exchange of urinary $Na^+$ and $NH_4^+$ (Gilman, 1958). All of these appear to be dependent upon $Na^+$ and $H^+$ exchange. When the availability of hydrated $CO_2$ as $H_2CO_3$ is reduced by carbonic anhydrase inhibitors, the rate of $H^+$ transport is reduced, the reabsorption of $HCO_3^-$ is incomplete, urinary buffers are not acidified, and ammonia disappears from the urine.

The principal site of action of acetazolamide appears to be in the *renal tubules where carbonic anhydrase is inhibited.* There is specific interference with the production of hydrogen and bicarbonate ions. The impeding of this acidification process, which conserves base, results in a copious diuresis of bicarbonate, sodium and potassium ions, and water. Thus one observes that acetazolamide functions as a diuretic by a mechanism which may account for a facet of the renotropic action of chlorothiazide. Since acetazolamide produces a loss of sodium without a concomitant loss of chloride, its action is synergistic with that of the organic mercurials which produce chloruresis. On the other hand, the effect of acetazolamide is partially blocked by the acidifying diuretic ammonium chloride.

Although acetazolamide is useful as a diuretic in edema of cardiac origin, its action does not appear to be as dependable as that of chlorothiazide or the mercurial diuretics. When acetazolamide is used in conjunction with mercurial diuretic therapy, it is important to administer potassium chloride to prevent potassium depletion and hypochloremic alkalosis (Weston, 1957).

In the treatment of glaucoma, acetazolamide is considered a most useful systemic drug and a valuable adjunct to the localized treatment with pilocarpine and other cholinergic agents. The two approaches are synergistic. In glaucoma, the rapid action of acetazolamide suggests a direct effect on the secretory mechanism of the ciliary processes as follows:

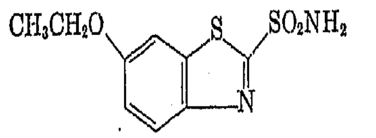
1. $CO_2$ anhydrase provides cells with $H_2CO_3$ to neutralize $OH^-$.
2. In the formation of aqueous humor $Na^+$ passes from blood through ciliary epithelium and $H^+$ passes back into blood.
3. Net result is excess of $OH^-$ in cell.
4. With diminished $H_2CO_3$, $OH^-$ in cell augments pH.
5. With elevated pH in the ciliary cells, inhibition of secretory process occurs.

**Therapeutic use of acetazolamide.** Acetazolamide is used to produce diuresis in edema of cardiac origin. It is given orally once a day in 250-mg. tablets. The studies using this diuretic which have come to our attention indicate that it is usually effective. Its side reactions are few and generally transitory and reversible. The side effects which have been encountered are *paresthesias, drowsiness, mild acidosis, fever, drug rash,* and *occasional disorientation* with high dosage levels. Pearson *et al.* (1955) reported a case of fatal agranulocytosis in a 66-year-old woman following acetazolamide therapy. Glushien and Fisher (1956) reported a case of renal lesions of the sulfonamide type after treatment with acetazolamide. Acetazolamide is interdicted in patients with electrolyte imbalance resulting from emesis, diarrhea, hyperchloremic acidosis, and all types of adrenal failure. Since the discovery of the thiazides, acetazolamide is seldom used in edema of cardiac origin.

Webster and Davidson (1956) demonstrated that acetazolamide is capable of inducing impending hepatic coma in susceptible alcoholics with cirrhosis. The impending coma appeared to be associated with femoral or antecubital vein blood-ammonia-nitrogen concentrations at levels above those seen in mentally clear patients with cirrhosis.

Other indications for acetazolamide therapy are *premenstrual tension,* (see page 787), *petit mal epilepsy,* and *glaucoma.*

**Ethoxzolamide (Cardrase).** This is another carbonic anhydrase inhibitor similar to acetazolamide. Its structure is shown in the formula:



Ethoxzolamide
(6-ethoxybenzothiazole-2-sulfonamide)

The action and uses of ethoxzolamide are similar to those of acetazolamide. It appears to be about twice as potent and to enjoy the same duration of action. The drug is used as a mild diuretic in the control of petit mal epilepsy, and in the treatment of glaucoma. It is usually well tolerated. The side effects encountered are nausea, dizziness, numbness, and paresthesias. Drowsiness, fatigue, headache, and xerostomia less frequently occur. Prolonged use in glaucoma may induce anorexia and weight loss.

Ethoxzolamide is available in tablets of 62.5 and 125 mg. The usual dose in glaucoma is 1 to 2 tablets 2 to 4 times daily, preferably on alternate days. In petit mal epilepsy up to 750 mg. have been given daily in divided doses.

**Diuresis and aldosterone antagonists.**

Steroidal chemists have synthesized compounds that are specific antagonists to the renal tubular action of aldosterone. One of these is the steroid *Spironolactone* or *Aldactone A*. Chemically Aldactone A is a 3-(3-oxo-7-$\alpha$-acetylthio-17$\beta$-hydroxy-4-androsten-17$\alpha$-yl) propionic acid $\gamma$-lactone. These compounds are characterized by lactone groups at position "17" and are called 17-spirolactones. Aldactone A is active biologically only insofar as it blocks the action of aldosterone. Its principal action is manifested on the tubular electrolyte action of aldosterone and emulates the abrupt withdrawal of aldosterone. These effects on the renal electrolytes are, in the main, as follows: increased urine volume and $Na^+$ and $Cl^-$ excretion, slight decrease in urinary $K^+$, marked decrease in $H^+$, and a moderate increase in urinary $NH_4^+$ excretion. All other types of diuretics increase to some degree the urinary excretion of $K^+$, Aldactone A evokes a decrease in $K^+$ excretion. Aldactone A does not appear to affect the proximal tubular reabsorption of $Na^+$; however the distal tubular reabsorption of $Na^+$ and secretion of $K^+$ is inhibited.

The diuretic action of Aldactone A is elicited gradually. It never produces an immediate copious diuresis; several days of therapy are required for the full diuretic effect. Aldactone A achieves its greatest success in *primary aldosteronism* as a specific antagonist. It does not alter the secretion of 17-ketosteroids or other steroids from the adrenal cortex. Its action is primarily that of combating the peripheral effects of aldosterone. Other clinical uses of Aldactone A appear to be in edematous states such as cirrhosis, nephrosis, or congestive heart failure, in which upon prolonged use of conventional diuretics the $Na^+$ and $Cl^-$ excretion is diminished and abnormally high amounts of aldosterone are being excreted. These patients respond well to Aldactone A medication. Aldactone A may be used in conjunction with chlorothiazide or mercurial diuretics. Since these agents mainly block the proximal tubular reabsorption and Aldactone A inhibits distal tubular reabsorption, the combination therapy evokes a synergistic diuresis.

Aldactone A is administered in daily doses of 100 mg. Side effects at this dosage level are rarely encountered. In doses that will exceed the usual daily dose, drowsiness and ataxia of several hours' duration have been observed. The untoward side effects of Aldactone A are minimal. Electrolyte imbalance may occur. No renal or hepatic toxicity of significance has been reported.

When first used, Aldactone was poorly absorbed from the gastrointestinal tract and hence the response was capricious. Aldactone A is identical chemically with Aldactone, but its physical properties have been modified to enhance absorption. The 25-mg. dose of Aldactone A appears to evoke a degree of diuresis equal to 100 mg. of Aldactone. Aldactone A is available in 25-mg. tablets.

**Nonsteroidal aldosterone antagonists.** It was observed by Wiebelhaus *et al.* (1961) that triamterene (2,4,7-triamino-6-phenyl-pteridine) evoked a natriuresis in rats without a potassium loss. The compound was more active than spironolactone. Triamterene was effective in the adrenalectomized animal without previously administering a mineralocorticoid. This suggested that its action on the exchange of $K^+$ and $Na^+$ may be more direct than through aldosterone antagonism.

Triamterene was used first in man by Crossley *et al.* (1961) in doses of 50 to 300 mg. daily. The drug was well absorbed and appeared in the urine within 15 to 30 minutes after ingestion. The peak excretion rate was in 6 to 8 hours and the duration of effect was 24 hours. The onset of natriuresis was prompt and a reduction in potassium excretion occurred. Similar results were reported by Laragh *et al.* (1961).

It appears that the clinical application of an agent like triamterene is in conjunction with thiazide therapy. Accordingly, Heath and Freis (1963) used the agent with hydrochlorothiazide in the treatment of hypertension. They suggest that the action of triamterene is due only partially to aldosterone antagonism. It was observed that the combined use of the drugs evoked about the same degree of natriuresis with much less potassium loss than did the thiazide alone. The control of hypertension was as effective with the combination of drugs as with hydrochlorothiazide alone. The sole advantage appeared to be the prevention of hypokalemia. No side effects from triamterene were encountered.

It is the opinion of the authors that the advantage achieved by the use of triamterene is slight and that the drug is destined to enjoy a limited field of usefulness.

**Mercurial diuretics.**

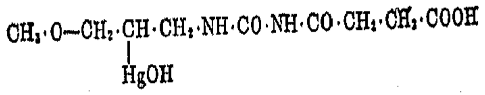
**Historical development.** For many centuries the salts of univalent and divalent mercury have been known to elicit diuretic responses. Paracelsus used calomel (mild mercurous chloride) as a cathartic and diuretic. Richard Bright administered calomel to his edematous patients until salivation was produced. The famous Guy's Hospital Pill contained digitalis, squill, and calomel.

Jendrassik (1886) demonstrated that calomel produced diuresis with marked chloride excretion in patients with edema of cardiac origin. The concomitant diarrhea seriously limited the use of calomel as a diuretic.

The modern era of the mercurial diuretic begins with use of organic compounds containing divalent mercury. These substances do not produce $Hg^{++}$ ions, and their dosage and administration can be more easily controlled. Saxl and Heilig (1920) demonstrated the marked diuretic action of the organic mercurial known as *Merbaphen.* Mersalyl was introduced in 1924 and because it was less toxic soon replaced merbaphen. Soon other organic mercurials followed with lower toxicity and other advantages over these earlier drugs.

**The official mercurial diuretics.** The following mercurial diuretics are recognized in the Pharmacopeia:

*Meralluride* is official as methoxyhydroxymercuripropylsuccinylurea, as shown in the formula, with a molecular equivalent of theophylline.

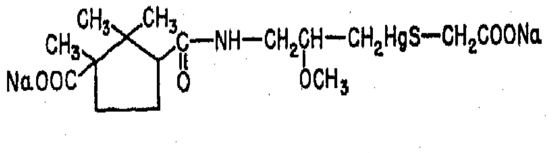


$$CH_3\cdot O{-}CH_2\cdot \underset{\displaystyle HgOH}{\underset{|}{CH}}\cdot CH_2\cdot NH\cdot CO\cdot NH\cdot CO\cdot CH_2\cdot CH_2\cdot COOH$$

Meralluride, U.S.P.
Mercuhydrin

An injection is also official which contains the mercurial and theophylline made soluble by the addition of sodium hydroxide. The mercurial contains 31 to 33 per cent of mercury.

*Mercaptomerin (Thiomerin).* Chemically, mercaptomerin is N-($\gamma$-carboxymethylmercaptomercuri-$\beta$-methoxy)propyl camphoramic acid disodium salt. Its structure is shown in the accompanying formula.



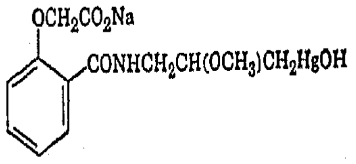
Mercaptomerin, U.S.P.
Thiomerin

It will be observed that structurally mercaptomerin differs from mercurophylline by the replacement of the theophylline molecule by the monothiol, sodium thioglycolate.

An examination of the foregoing formulas reveals that each of the mercurial diuretics is a somewhat complicated organic molecule containing a divalent mercury atom attached to carbon. The mercury atom is combined also with an hydroxyl group. The mercury in this combination is inappreciably ionized, and hence, although it serves as a tubule irritant in effective concentrations, it is not a tubule poison like mercuric chloride.

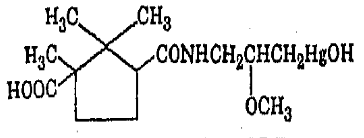
The National Formulary recognizes the following mercurial diuretics.

*Mersalyl* contains from 38.5 to 40.5 per cent of mercury. The compound is also recognized in 2 dosage forms, namely, *mersalyl and theophylline injection* and *mersalyl and theophylline tablets.*



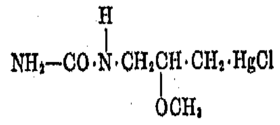
Mersalyl, N.F.
Salyrgan

*Mercurophylline* is official as the sodium salt of the foregoing compound with a molecular equivalent of theophylline. As recognized, it contains from 37 to 42 per cent of mercury. An injection and tablets are also official.



Mercurophylline, N.F.
Mercuzanthin, Mercupurin

**Other mercurial diuretics.** *Chlormerodrin (Neohydrin).* In 1950 Rowland *et al.* reported the synthesis and pharmacologic study of a number of new organic mercurials. The compounds structurally were chloromercuri-alkoxy-propyl-urea derivatives. Certain of these compounds evoked a greater diuretic response in animals than the generally used mercurial diuretics. Outstanding in the series was 3-chloromercuri-2-methoxypropylurea (Neohydrin), as shown in the accompanying formula.



$$NH_2{-}CO\cdot\overset{H}{N}\cdot CH_2\underset{OCH_3}{CH}\cdot CH_2\cdot HgCl$$

Neohydrin

Neohydrin has taken its place among the most popular mercurial diuretics and offers the striking advantage of a high degree of therapeutic effectiveness upon oral administration. It will be observed that chemically Neohydrin is a comparatively simple molecule.

**Mercurial diuretics and theophylline.** It is a recognized practice to administer the organic mercurials with a molecular equivalent of theophylline. The available dosage forms of certain of the mercurial diuretics represent this combination. DeGraff and Batterman (1935) demonstrated that the presence of theophylline diminished the toxicity of mercurial diuretics at the injection site. Furthermore, these investigators (1938) showed that the presence of theophylline enhanced the absorption of the mercurial compound from the injection site in skeletal muscle. DeGraff and his associates (1938) observed that the optimal amount of theophylline corresponded to a mole equivalent of the monohydrate of theophylline to each mole of the mercurial diuretic. There is evidence to show that compound formation occurs between the 2 compounds. Theophylline combinations with the organic mercurials were shown by DeGraff *et al.* (1938) to influence the excretion of the mercury injected. The percentage of the administered mercury which is excreted within 6 hours is increased from 30 to 40 per cent by the simultaneous administration of theophylline if the injection is intravenous. Upon intramuscular injection it increases from 100 to 300 per cent with theophylline.

**Mechanism of action of the mercurial diuretics.** It is generally accepted that the mercurial diuretics exert their effect by reducing tubular reabsorption of water. However, the extrarenal effects of the compounds were believed at one time to play an important part in mercurial diuresis. The classical experiments of Govaerts (1928) demonstrated the specific renal effect of the drugs. He transplanted a kidney from an animal undergoing active mercurial diuresis into the region of the neck of another animal. The vessels were anastomosed, and the kidney continued to undergo active diuresis although its blood supply was from a normal animal. In the same manner a normal kidney failed to show diuresis when transplanted into the neck of a dog whose intact kidney was exhibiting mercurial diuresis.

Bartram (1932) demonstrated a unilateral diuretic response when the mercurial diuretic was injected into one renal artery.

Kidney function was measured by means of creatinine and urea clearance. In addition, by means of a thermostromuhr, renal blood flow was measured. In these studies neither renal blood flow nor glomerular filtration rate was influenced by mersalyl diuresis. The diuresis resulted from the diminished tubule reabsorption of water. Dicker (1946), using rats, concluded that the mercurial diuretics also diminished the glomerular filtration rate.

The weight of evidence favors the hypothesis that the mercurial diuretics act through diminution of tubular reabsorption of water. Inorganic mercurous and mercuric salts diminish tubular reabsorption of water and produce diuresis. This is not achieved by these salts, however, without specific tubular damage. The organic mercurials diminish tubular reabsorption by virtue of the action of the organomercuric complex R-Hg$^+$ and do not concomitantly produce tubular damage. Leff and Nussbaum (1957), in reviewing their extensive laboratory and clinical experience with organomercurials, state: "This clinical and laboratory investigation disproves the fear of an 'inorganic mercury' effect from the retention of massive cumulative doses of parenteral and oral organomercurials."

Mercurial diuresis produces a marked increase in chloride excretion in the urine. Mercurial diuretics elicit a powerful action in the depletion of the tissue salt content, total plasma base, and plasma BHCO$_3$. The diuresis, which is actually a "saluresis," is the first stage of the toxic effect on the renal tubules of mercury. The increased urinary excretion of chloride is accompanied by increased amounts of sodium. Large doses of the organic mercurials inhibit the excretion of potassium. It is proposed that the effect stems from the blocking of the reabsorption of potassium in the proximal and distal nephron and also from the inhibiting of the secretion in the distal segment.

Gardier and Woodbury (1955) studied the action of mercaptomerin in dogs with respect to the renal excretion of bicarbonate. There appeared to be no significant effect of the mercurial upon the reabsorption of bicarbonate from the distal tubule. The site of action appeared to be the proximal tubule. It is suggested that the reduction in chloride reabsorption evoked by mercurials is the result of proximal tubular inhibition.

An interesting contribution to the mechanism of action of the organic mercurials was made by Grossman *et al.* (1955). They administered vasopressin to individuals to produce a hypertonic urine of low volume. Upon the administration of mercaptomerin, excretion of urine slightly exceeding isotonicity ensued. This suggests that the mercurial produces an effect of adding a relatively large volume of isotonic urine to the previously small volume of hypertonic urine. The fact that mercurial diuresis is isotonic suggests that the principal site of action is proximal to the segment of the nephron at which *anisosmotic* or free water reabsorption occurs. Thus the cessation of action of a mercurial diuretic may reflect either the elimination of the drug or possibly the activation of compensatory countermechanisms providing for fluid retention.

**Mercurial diuretics and enzyme systems.** The evidence available indicates that the mercurial diuretics readily penetrate tissue cells. The compounds *appear to be adsorbed by cell constituents in the vicinity of the active enzyme systems and to produce their inhibition by slowly making available mercuric ions.*

It is well established that mercuric ions combine with sulfhydryl enzyme systems (see page 950). Sulfhydryl enzymes are hydrolytic and oxidative in nature and are intimately associated with carbohydrate, fat, and protein metabolism. Indeed, approximately 90 per cent inhibition of sulfhydryl enzymes is effected by concentrations of $10^{-5}$ M of mercuric chloride (Barron and Kalnitsky, 1947).

The specificity of the mercurial diuretics for sulfhydryl-bearing proteins in the kidney structure appears to be established. Cafruny *et al.* (1955) demonstrated that diuretic doses of mersalyl reduced cytoplasmic protein-bound sulfhydryl concentrations in the cells of the terminal portions of the proximal tubules and their brush borders, loops of Henle, and medullary collecting ducts. The straight portions of the proximal tubules exhibited the most rapid response. BAL was capable of inducing a reversal of the response. Thus evidence points again to the specific effect upon the proximal tubule, where the effect of the mercurial upon protein-bound sulfhydryl groups may be responsible for the suppression of the reabsorptive mechanism.

The experiments of Miller and Farah (1962) have contributed further to the knowledge of the mechanism of action of the mercurial diuretics. A nondiuretic organic mercurial, *p*-chloromercuribenzoic acid (CMB), was injected into dogs. The mercury of CMB in the renal cortex blocked the action of mercurial diuretics. They propose that the SH group is an integral part of the mercury receptor site, but not *per se* the cause of diuresis. The SH serves as an anchoring group and permits the mercury to combine with a second receptor site to provoke diuresis. The nature of the group in the second receptor site is not known. If the SH anchoring group is blocked by a nondiuretic mercurial, a mercurial diuretic fails to evoke diuresis.

**Mercurial and acidotic diuretics.** It is well known that the mercurial diuretics are much more effective after the administration of such acidotic diuretics as ammonium chloride. The combined effect of the 2 types of diuretics is greater than the sum of their actions individually. In normal individuals the organic mercurial diuretic produces diuresis with concomitant decrease in plasma volume of about 13 per cent. Serum proteins increase correspondingly about 15 per cent. Further dehydration appears to be at the expense of the tissue water, as the increased concentration of serum protein supports plasma volume in spite of tissue dehydration. It appears, therefore, that the fluid lost in diuresis by the mercurial diuretic is mainly interstitial water. When the acidotic type of diuretic is combined with the mercurial, the fluid loss extends to the cellular water to a greater degree than when the mercurial alone is used.

Ammonium chloride supplies an abundance of chloride ions which are a contributing factor for continued diuresis. Weston (1957) showed that acidification of the urine by the administration of ammonium chloride was a critical factor in augmenting mercurial diuresis. This appeared to be more important than the hyperchloremia elicited by ammonium chloride, since acidification of the urine by the administration of ammonium nitrate also enhanced mercurial diuresis. The mechanism by which urinary acidification augments mercurial diuresis is not known. However, Weston suggests that some mercurial effect on the distal tubular processes also may be exerted during the course of the potentiated diuresis. This provides a working hypothesis for combined acidotic and mercurial diuresis. According to the work of Gardier and Woodbury (1955), the prime site of action of a mercurial diuretic is the proximal tubule; upon the acidification of the urine enhanced diuresis may be achieved by the extension of the inhibition of tubular reabsorption to the distal tubule.

Ammonium chloride also rapidly restores the electrolyte balance in chloride depletion produced by mercurial diuresis. Furthermore, hypochloremia and its sequelae are prevented.

**Toxicity of the mercurial diuretics.** The toxicity of the ionizable salts of mercury is a matter of common knowledge (see page 206). The organic mercurials which are capable of evoking diuresis share this toxicity. The degree of toxicity, however, is greatly diminished by the presence of the mercury in an organic molecule. There are numerous reports in the literature concerning severe toxic manifestations and deaths resulting from the injection of mercurial diuretics (Lehman, 1947).

DeGraff and Nadler (1942) divided the toxic manifestations of the mercurial diuretics into 2 classes: (*1*) *those associated with the diuresis, and* (*2*) *those directly related to the inherent toxicity of the drug.* Toxic manifestations of the first class are those associated with electrolyte imbalance produced by the diuresis. Effective mercurial diuresis appears to depend upon an available supply of water and chloride in the tissues. Symptoms of chloride depletion may occur therefore after mercurial diuresis. The syndrome is similar to that which occurs in chloride loss during heat prostration. *Weakness, apathy, somnolence, disorientation, delirium,* and occasionally *coma* may result. Since most of the individuals receiving the mercurial diuretics are cardiac patients on a low sodium diet, acute sodium depletion should be meticulously avoided. The margin of safety between blood sodium depletion and acute *hyponatremia* is narrow. Electrolyte imbalance may lead to increasing edema with oliguria and even anuria. It is therefore evident that unless the electrolyte and water balances are carefully controlled, symptoms may follow the use of the mercurial diuretics which are the result of the intended action of the drug and not untoward side effects.

The second class of toxic effects of the mercurial diuretics is attributed to *the direct action of the drugs themselves.* These compounds are powerful therapeutic agents, and many types of idiosyncratic reactions arise. We shall review here only the predominating toxic manifestations.

The actions which appear to be most directly related to the mercury are gastrointestinal and renal symptoms. The gastrointestinal symptoms are typically those of mercury, namely, *salivation, stomatitis,* and *hemorrhagic colitis.* The kidney changes result from the action of renal irritation involved in the production of diuresis. These changes are in the following order: (1) casts, hyaline and granular, (2) albumin, (3) leukocytes, and (4) erythrocytes. Brown and Englebach (1936) made counts of urinary casts in 5 patients with ascites who had no evidence of renal disease. After clinically effective doses of mersalyl, the count was appreciably elevated in each case. The effect, however, was transient.

Acutely fatal results from the mercurial diuretics have been reported by various authors. The acute cardiac effects of these compounds have been studied by Lehman (1947). Organic and inorganic mercurials have been observed to act directly upon the heart, especially upon intravenous injection. They produce marked changes in rhythm and conduction. Long and Farah (1946) showed that mercurials diminished the work capacity of the myocardium.

Ruskin *et al.* (1949) electrocardiographically studied the cardiotoxicity of several mercurial diuretics on the isolated rabbit's heart. Mercaptomerin was calculated to be 200 times less toxic to the myocardium than mercuhydrin, and 1000 times less toxic than mersalyl-theophylline. The cardiotoxicity of mercaptomerin could be prevented by the previous administration of BAL [2,3-dimercapto-1-propanol]. The administration of ascorbic acid was found to prevent the slight cardio-conduction effects of mercaptomerin.

The inherent toxicity of the mercurial diuretics should be borne in mind during their clinical application. Nevertheless, these substances are dependable and useful therapeutic agents. Furthermore, when one compares the toxic manifestations with the large number of successful uses of the drugs without unfavorable side effects, the compounds appear to be reasonably safe. For example, in their review of toxic manifestations from the mercurial diuretics, DeGraff and Nadler found no deaths reported from the rectal or intramuscular use of the drugs. Leevy and White (1951) stated that they had given 13,000 injections of mercurial diuretics during a period of 4 years without any ill effects.

Brown (1955) recognized a small number of patients who were truly allergic to the mercurial diuretics. Patients whose history suggests that they might be "drug reactors" should be treated with special precaution. Sensitivity to 1 mercurial diuretic, however, does not necessarily bespeak sensitivity to this class of agents.

Farah and Maresh (1948) studied the effect of BAL (see page 950) upon the toxicity and diuresis produced by mersalyl in dogs and rabbits. They observed that about ½ mole of BAL abolished the diuretic action of 1 mole of mersalyl. Of special interest is their observation that the monothiols cysteine and glutathione do not abolish the diuretic action of mersalyl but protect the myocardium against the toxic action of the compound. These investigators showed a direct correlation between the initial decrease in urine flow following the intravenous injection of mersalyl, with a decrease in renal volume and decrease in renal blood flow. This incipient antidiuretic action of the mercurial diuretic was abolished by the mono- and dithiols.

**Distribution and excretion of the mercurial diuretics.** The mercurial diuretics enter the blood stream from the various avenues of entrance to the body. Here combination occurs between the mercurial and serum albumin. There is evidence to indicate that 2 molecules of albumin unite with 1 atom of mercury. From the blood protein combination the mercurial is distributed to the various organs of the body. During the period of active excretion of the mercurial, high concentrations of mercury are found in the liver and kidneys. Lesser concentrations are present in the muscles and bones. Following this period of active excretion, the levels of mercury in the muscles and kidneys are reduced to very low values. On the other hand, the liver and bones retain mercury for long periods. By shifting the acid-base equilibrium of the blood to the acid side, the mercury stored in the bones is mobilized, and an increase in plasma concentration is produced.

When administered parenterally, the mercurial diuretics are excreted mainly by the kidneys. A portion of the mercurial is excreted by the gut, and trace quantities may be detected in the saliva and sweat. When administered orally, larger quantities of the mercurials are excreted by the gut largely owing to poor intestinal absorption. Many factors control the rate of excretion of the organic mercurial. Data extant in the literature indicate that within 24 hours after a therapeutic dose from 60 to 100 per cent is excreted. Indeed, it appears quite evident that trace quantities of mercury remain in the tissues for much longer periods of time.

Not all of the mercurial diuretics are excreted at the same rate or in the same form. For example, Moyer *et al.* (1957b) observed that meralluride was excreted in the urine unchanged to the extent of 95 to 99 per cent. Weiner and Muller (1955) presented evidence to show that Salyrgan is excreted in a complex with 1 or more thiols of low molecular weight. This complex is considered to be a product of detoxification.

**Choice of a mercurial diuretic.** There appears to be convincing evidence to indicate that the most satisfactory mercurial diuretics available today are meralluride (Mercuhydrin) and mercaptomerin (Thiomerin). However, it is difficult to determine which of the 2 is the better. Indeed it appears that one of the compounds may meet the individual needs of one patient, whereas the other is more effective in another patient.

Effective diuresis is not the only requirement of a satisfactory mercurial diuretic. Availability by various avenues of entrance to the body is an important consideration. Absence of reactions at the site of parenteral administration is likewise a vital factor.

Meralluride is available in tablets for oral administration. It has been observed that by mixing meralluride with ascorbic acid its effectiveness as an orally available mercurial diuretic is materially increased. Thus, Shaffer *et al.* (1950) found that a tablet containing 60 mg. of meralluride (equivalent to 19.5 mg. Hg) and 100 mg. of ascorbic acid, was the therapeutic equivalent of a tablet containing 120 mg. of meralluride alone. This represents a distinct and interesting advance in oral mercurial therapy. It appears to have been substantiated in various clinics; however, the mechanism of action of ascorbic acid remains obscure.

The development of Neohydrin has done much to alter the physician's choice of a suitable diuretic agent. Several competent investigators have confirmed its diuretic efficacy when administered orally. Greiner and Gold (1952) found that the tablet of Neohydrin evoked a diuretic response equivalent to ¾ of that of a standard injection of meralluride. The untoward reactions of the drug are few. Moyer *et al.* (1952) observed gastrointestinal symptoms in about 10 per cent of the patients taking Neohydrin.

Neohydrin is available in tablets containing 18.3 mg. of the mercurial, 3-chloromercuri-2-methoxy-propylurea (see page 806). The usual dosage schedule is 1 or 2 tablets 3 times daily.

Indeed from the foregoing data and other available information, it appears that the 2 official mercurial diuretics meralluride and mercaptomerin are in most hands equally efficacious for parenteral therapy. There does not appear to be strong sentiment which favors one agent over the other.

Neohydrin appears to be the drug of choice as an orally administered mercurial diuretic at present. Success with Neohydrin therapy has been confirmed in many clinics (Moyer *et al.*, 1953; Leff and Nussbaum, 1957; and Kaplan *et al.*, 1953). Neohydrin has in many cases completely replaced parenteral therapy and in others served as a useful adjunct to it.

Finally, the success in therapy with any of the mercurial diuretics discussed is often dependent upon the correction of the basic physiologic needs of the patient. Bed rest, adequate digitalization, correction of electrolyte imbalance, and maintenance of adequate blood volume and circulation are essential as the extracellular fluid is being diminished by the mercurial-induced diuresis.

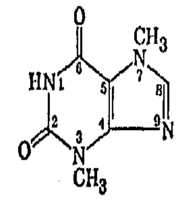
Despite the fact that the mercurial diuretics have a long and successful history as dependable diuretics, their use is definitely waning. As mentioned before, this is due to the widespread use of chlorothiazide and hydrochlorothiazide. The mercurial diuretic may often be used parenterally to initiate diuresis and then maintenance of diuresis is achieved by hydrochlorothiazide. Furthermore, the mercurial diuretic is a dependable reserve diuretic for the small segment of patients who are refractory to the action of hydrochlorothiazide or who develop a tolerance to the drug. It appears that the mercurial diuretics and the thiazides elicit their effects on $H^+$-$Na^+$ exchange mechanisms and $Na^+$-$K^+$ interrelationship, and their simultaneous administration to the same individual may be advantageous. A greater degree of saluresis may be obtained without the production of hypokalemia. The distinct advantage of the mercurial diuretic appears to stem from its immediate effect upon parenteral administration when prompt diuresis is imperative.

The principal use of the mercurial diuretics is in the treatment of edema accompanying congestive heart failure. For a detailed discussion of their use, see page 1096 in the 4th edition of this text.

### The xanthine diuretics.

The 3 official methylated xanthines have been discussed previously (see page 471). They are *caffeine*, *theophylline*, and *theobromine*. As a cerebral stimulant caffeine is the drug of choice. The value of theophylline as a vasodilator was discussed (see page 670). Theophylline is a more powerful diuretic than theobromine. Nevertheless, the action of theobromine is more sustained, and hence it appears to be the methylated xanthine of choice as a diuretic. Theobromine also appears to be better tolerated by the stomach than theophylline.

Theobromine is 3,7-dimethylxanthine, as shown in the accompanying formula.



Theobromine
(3,7-dimethylxanthine)

Theobromine is very insoluble in water; it is made soluble by mixing it with the alkali salts of organic acids such as acetic and salicylic. The sodium acetate dosage form is official.

**Theobromine and Sodium Acetate, N.F.** This mixture contains about 58 per cent of theobromine. The remainder is sodium acetate. It is a white, crystalline powder which is readily soluble in water. It is alkaline to phenolphthalein.

Theobromine is not absorbed readily from the gastrointestinal tract when administered alone. However, when it is mixed with sodium acetate the xanthine is quite readily absorbed. Although theobromine shares with caffeine the action of cerebral stimulation, its central action is mild. Theobromine also shares with theophylline the property of stimulating the heart muscle and also causing vasodilatation. These responses are not so marked as those evoked by theophylline. Therefore we shall give consideration to theobromine primarily as a diuretic. In this capacity the compound still enjoys a limited use. Its action is far less dramatic and dependable than that of the thiazides or the mercurial diuretics.

**Diuretic action of theobromine.** V. Schroeder (1887) was the first to demonstrate the diuretic action of the methylated xanthine. He attributed the response to a direct renal action, owing to the fact that he was unable to demonstrate that the fluid in the tissues was markedly changed by the action of the xanthines.

Although the methylated xanthines tend to increase the glomerular filtration rate by improving the general circulation, or specifically the renal circulation, this effect is not a prime factor in their diuretic action. By means of inulin-clearance studies, it was shown that the methylated xanthines did not alter the total quantity of inulin excreted. However, it was demonstrated that the concentration of the inulin in the urine diminished under the diuresis. This is strongly indicative of diminished tubule reabsorption of water from the glomerular filtrate as the mechanism of action.

The activity of aminophylline as a diuretic in dogs and man was studied by Nechay (1961). He observed that the urinary pattern of aminophylline diuresis was similar to that of chlorothiazide. The renotropic action was unaffected by metabolic acidosis and probably increased by alkalosis. The action was additive when hydrochlorothiazide or mercaptomerin was given simultaneously in maximal effective doses. Presumably the mechanism of the diuretic action of the 3 methylated xanthines is the same.

**Therapeutic uses of theobromine.** As has been previously stated, the diuresis produced by the methylated xanthines is not so prompt, dependable, or uniform as that elicited by hydrochlorothiazide or the mercurial diuretics. The principal use of theobromine as a diuretic therefore, is in cases of edema with renal insufficiency.

The mixture of theobromine and sodium acetate is given generally in capsules of 0.5 gm. A daily dosage of 3 to 4 gm. is often necessary for full diuretic effect. Frequently tolerance is acquired, but it may be broken by a short period of drug withdrawal.

Theobromine calcium salicylate, recognized by the National Formulary, is claimed to be tolerated better than the sodium acetate combination. Indeed it appears to present the distinct advantage of not adding additional sodium to the daily intake of patients suffering with edema.

### Acidotic diuretics.

The acidotic diuretics ammonium chloride and calcium chloride have been previously mentioned. The former has almost completely replaced the latter salt as a diuretic. It is used alone or to intensify the action of mercurial diuretics.

**Ammonium Chloride, U.S.P.** This salt is a white, crystalline powder. It is somewhat hygroscopic. It does not emit the odor of ammonia. One gram dissolves in 2.6 ml. of water. The pH of a molar solution of ammonium chloride is 4.6.

The salt is readily absorbed from the gastrointestinal tract. It produces irritation, and in doses sufficient to elicit diuresis (4 gm. daily) it is most effectively given in enteric-coated capsules.

*Diuretic action of ammonium chloride.* The ammonium chloride absorbed from the gastrointestinal tract is converted by the liver into urea and hydrochloric acid. Urea has no acid-consuming power. The hydrogen ions from the newly-formed hydrochloric acid alter the $BHCO_3:H_2CO_3$ ratio of the blood by union with $BHCO_3$. The reduction of the alkaline reserve lowers the capacity of proteins in the tissues to bind water, fluid moves from the tissues to the blood, and diuresis occurs. In chronic interstitial nephritis, where the capacity of the kidney to produce ammonia is diminished, a similar type of acidotic diuresis takes place.

Binger and Keith (1933) observed that the use of ammonium chloride or nitrate as diuretics may give rise to a moderate degree of renal insufficiency. The effect, however, is transient. They proposed that the renal insufficiency results from the acidotic condition produced by the salt. The special advantage of ammonium chloride as a diuretic is in edemas where chloride plasma has been markedly reduced. In severe uremia the ammonium salts are obviously interdicted.

*Other uses of ammonium chloride.* This salt has been used for years in small doses of 0.2 to 0.3 gm. as an expectorant in coughs and bronchitis. Perry and Boyd (1941) found the salt to increase mucus secretion from the bronchial glands in animals only when the dose was higher than it was possible to achieve in therapeutics. The value of the salt as an expectorant rests upon a rather doubtful basis.

The salt is used in alkalosis to mobilize calcium ions, and its effect here is dependent upon the production of incipient acidosis. Zintel *et al.* (1943) administered the salt intravenously in severe alkalosis. They gave a 2 per cent solution of ammonium chloride in normal saline or 5 per cent dextrose solution. It is claimed that 1 gm. of the salt reduces the carbon dioxide-combining power of the serum in a 70-kg. individual by 1.1 volume per cent.

*Therapeutic uses of ammonium chloride.* The principal use of ammonium chloride is to induce incipient acidosis for the purpose of diuresis, calcium mobilization, or to combat alkalosis. As a diuretic the salt is used mainly to intensify the action of the mercurial diuretics and occasionally in premenstrual tension. It may be also used to supply plasma chloride in cases of edema where the chloride level of the plasma is low.

Keith (1936) recommends a 10-gm. daily divided dose of ammonium chloride. This is far in excess of the Pharmacopeial dose and often produces disconcerting symptoms such as skin rash, extreme fatigue, and anorexia. The official daily dose of 4 gm. appears to be more desirable. The salt is given in enteric-coated capsules or tablets of 0.5 gm. each.

Ammonium chloride is used in premenstrual edema. During this period there is marked sodium retention, and the urine output is reduced. The salt is given in divided doses of 3 gm. daily for 4 to 5 days prior to menstruation.

Ammonium chloride is also recommended in the acute attacks of Ménière's syndrome. The partial tissue dehydration produced by the salt appears to be useful in mitigating the vertigo and tinnitus.

### Low kidney threshold diuretics.

**Potassium Nitrate, N.F.** Potassium nitrate is a white, crystalline substance which is stable in air; 1 gm. dissolves in 3 ml. of water. This is an obsolete diuretic. For a description of its use see page 1237 of the 5th edition.

**Urea, N.F.** Urea is a white, crystalline powder; 1 gm. dissolves in 1.5 ml. of water. Its solutions are neutral to litmus paper. Urea is used in renal clearance tests and as a diuretic in certain selected cases of cardiac and nephrotic edema (Thorn and Tyler, 1944). The dose may range from 4 to 20 gm., 1 to 5 times a day. The substance is dissolved in water and its taste is masked with fruit juice or acacia syrup.

Since the work of Javid (1958), urea has been used in the treatment of cerebral edema. Its use is similar to that of mannitol (see page 297). The compound is used in a 30 per cent solution injected intravenously. The average dose is 1 gm./kg. Shaw *et al.* (1962) compared urea and mannitol in dogs subjected to cerebral anoxia. Their results favor the use of mannitol; however, its use in this condition is also fraught with occasional severe reactions.

### Osmotic pressure diuretics.

In acute oliguric or anuric conditions such as result from poisoning with mercuric chloride or in cerebral edema, intravenous osmotic pressure diuretics are indicated. For this purpose glucose and mannitol solutions are used. They pass through the glomerulus and exert a high osmotic pressure in the tubule. Here they diminish water reabsorption and increase water excretion. Hence they serve as diuretics. Dextrose injection is the drug of choice.

**Dextrose Injection, U.S.P.** The sterile solution is usually available for the purpose of producing diuresis in 25 and 50 per cent concentrations. As a rule, from 50 to 100 ml. of a 50 per cent solution is slowly injected intravenously. Owing to complete lack of toxicity, when the solution is prepared properly and free from pyrogens, glucose is the compound of choice.

The use of intravenous mannitol is discussed on page 297.

### Miscellaneous diuretics.

**Mictine and Rolictine** are pyrimidinedione derivatives which enjoyed a limited use as diuretics before the discovery of chlorothiazide. Today their use appears to be eclipsed by the more dependable diuretics of the chlorothiazide group. For a detailed discussion of these diuretics, see page 1104 of the 4th edition of this text.

### Chemical Structure and Newer Diuretics

From the data in this chapter it is abundantly clear that since the advent of the thiazide diuretics many compounds with a variety of chemical structures exert a beneficial renotropic action. They therefore present the possibility of being used as diuretics. As the mechanisms of the ion exchange in the kidney unfold, it appears that many of these agents exert their actions at different sites in the renal tubules and are specifically involved with the suppression of reabsorption of one ionic species such as $Na^+$ or $K^+$. This has become a very fertile field of investigation for the organic chemist and the renal pharmacologist.

Thus Cannon *et al.* (1963) described the diuretic action of a derivative of phenoxyacetic acid [2,3-dichloro-4-(2-methylenebutyryl)phenoxyacetic acid]. This compound appears to bear no structural relationship to any of the currently used diuretics. This agent, known at present as MK 595, was administered to patients in daily doses of 100 to 200 mg. It was markedly effective in evoking sodium and water excretion in refractory patients with congestive heart failure or cirrhosis with ascites. They found the drug effective when other diuretics failed. Amazingly, MK 595 was additive to the currently used diuretics in its effect. These authors state: "Its unique mode of action supports the hypothesis that multiple discrete mechanisms for $Na^+$ retention are operative to varying degrees in diseases associated with edema formation." It will be of interest to see whether this drug, the use of which is in its incipiency, will become a competitive diuretic.

### Antidiuretic Principle of the Posterior Pituitary

In the foregoing discussions in this chapter, the principal aims of drug therapy have been to diminish edema through diuresis. We shall now turn our attention to the diametrically opposed clinical aim of combating the polyuria which occurs in *diabetes insipidus*. In this condition the posterior pituitary injection is used. As stated previously (see page 755), the posterior pituitary injection contains 2 important pharmacologic agents, namely, oxytocin, which contracts the uterus, and Pitressin or vasopressin, which is a pressor substance (Kamm *et al.*, 1928). The vasopressin fraction contains the *oliguric* principle, useful in the treatment of diabetes insipidus. Although the pituitary preparation of the Pharmacopeia elicits the oliguric response, the vasopressin fraction appears to be the drug of choice as an oliguric agent.

**Vasopressin Injection, U.S.P. (Pitressin).** Vasopressin injection is a sterile solution in water for injection of the water-soluble pressor principle of the posterior lobe of the pituitary body. Each milliliter possesses an activity equivalent to 20 U.S.P. posterior pituitary units. Each ml. is equivalent to 0.5 mg. of Posterior Pituitary Reference Standard.

**Circulatory effects of vasopressin.** Oliver and Shäfer (1895) were the first to observe that extracts of the posterior lobe of the pituitary evoked a pressor response upon injection. Vasopressin produces this effect. The rise in blood pressure is often preceded by a brief fall. Upon repeated injections the depressor component of the effect becomes more pronounced, and the pressure element diminishes. The pressor response is not so marked as that of epinephrine, but it is more sustained. The action is not obliterated by adrenergic blocking agents since it is musculotropic in character. The pressor response arises from capillary as well as arteriolar constriction. Grollman and Geiling (1932) observed that intramuscular injections of vasopressin in normal individuals caused a brief but marked *decrease* in *pulse rate*, *cardiac output*, and *oxygen consumption*. These were followed by a prolonged rise.

The fall in blood pressure seen in anesthetized animals upon repeated injection of vasopressin does not appear to be due to vascular relaxation, because it is not seen in perfusion experiments. It is likely due to progressive cardiac hypoxia resulting from coronary constriction which is elicited by the drug.

The circulatory response to vasopressin has been used clinically to support the blood pressure in cases of mild shock and circulatory failure resulting from the loss of normal tone of the peripheral arterioles. It has been used also to combat the depressor response of spinal anesthetics.

**Response of the gastrointestinal tract to vasopressin.** Vasopressin stimulates gastrointestinal motility by a direct musculotropic action. The response is not mediated through the parasympathetic nerves. It is used clinically in *postoperative gas distention* and *paralytic ileus*. As a rule 0.5 ml. of vasopressin intramuscularly is the dose employed. It may be repeated in 3 or 4 hours. The response of the intestinal tract to vasopressin in human beings rarely involves the stomach. The action on the duodenum and rectum is also slight. The principal site of action is the small intestine. The response of the intestine to vasopressin does not appear to be as constant and as uniform as that produced by neostigmine (see page 588). In recent years the latter is replacing vasopressin in this field.

The interesting action of vasopressin on the uterus is discussed on page 787.

**Action of vasopressin on urine flow.** The action of vasopressin on urine flow takes place in 3 distinct phases.

1. Initial anuria owing to ureteral spasm (15 to 20 minutes)
2. Brief diuresis owing to increased blood pressure and some vasodilatation of the afferent glomerular arterioles (20 to 60 minutes)
3. Oliguria owing to increased tubule reabsorption of water (begins in 1 to 2 hours, reaches a peak in 3 hours, and is sustained for about 10 hours)

The first 2 effects are of no clinical significance. The sustained oliguric action is the action which is clinically useful in combating the polyuria of diabetes insipidus.

Van den Velden (1913) observed the oliguric action of posterior pituitary preparations. The action has been the subject of much study and some speculation. It was postulated that the action was due to the effect of pituitary in preventing the absorption of water from the intestinal tract. Verney (1926) showed the oliguric effect could be produced in a heart-lung-kidney preparation of an animal. This observation contradicted the hypothesis that the action resulted from extrarenal factors.

Bjering (1934) showed that the oliguric action was not accompanied by a decreased glomerular filtration rate. Vasopressin increases tubular reabsorption of water and diminishes urine flow by this mechanism. Burgess *et al.* (1933) confirmed the site of action of the oliguric principle as the kidney tubules, principally the loop of Henle. In fish and amphibians where the loop is not well developed, the oliguric action of vasopressin was found to be absent. The action was observed to increase in man and other mammals, presumably paralleling the development of the loop of Henle.

No one has achieved the separation of the substances responsible for the pressor and the oliguric actions of the extracts of the posterior pituitary. It is likely that the 2 responses are elicited by the same substance. In addition to stimulating the tubule reabsorption of water, the antidiuretic principle inhibits the reabsorption of chloride and sodium ions. On the other hand, phosphate reabsorption is stimulated. The inhibition of sodium and chloride reabsorption appears to be due to the presence of small quantities of oxytocin present as a contaminant in vasopressin. It is most effective in persons who are well hydrated.

**Assay and fate of vasopressin.** Vasopressin, as has been stated previously, is standardized by its pressor response on animals. This is compared with the activity of Posterior Pituitary Reference Standard.

The antidiuretic activity may also be assayed on animals. Lindquist and Rowe (1949) used the rabbit to assay the antidiuretic activity of vasopressin. They found this method superior to the former methods.

Larson (1938) carried out studies which indicate that enzyme processes in the liver and kidney attack vasopressin and terminate its activity. It appears that the amino-polypeptidase of the tissue ereptases inactivates vasopressin.

**Use of vasopressin in diabetes insipidus.** Diabetes insipidus is a rare disease. It is characterized by the excretion of large volumes of dilute urine. It is caused by organic disease of the central nervous system such as tumors of the brain in the region of the pituitary gland, head injuries, or infections. The disease appears to result from some interference with the physiologic chain of events which leads to the release of the antidiuretic hormone (ADH) from the neurohypophysis and its action on the cells of the renal tubules. Most of the cases of diabetes insipidus result from lesions interfering with the release of ADH; few have been encountered in which the refractoriness of the renal tubules to the action of ADH is the basic defect.

The volume of urine varies from 5 to 20 L. daily. This induces polydipsia and severe tissue dehydration. *Chills*, *gooseflesh*, *mottling of the skin*, *tremors*, *nausea*, *vomiting*, and *headache* are other symptoms resulting from water deprivation of the tissues. It is not desirable to check the water intake because when this is done, the tissue dehydration is aggravated because of continued diuresis.

The therapy is replacement of the oliguric principle of the posterior pituitary by vasopressin.

The injection of vasopressin (or posterior pituitary injection) checks the polyuria of the diabetes insipidus. The oliguric principle is absorbed also from the nasal membranes; the preparation has been successfully used as a spray and the powder as a snuff (Smith, 1934). Although the utilization is not efficient by this route of administration, it may be advantageously used to supplement the injections. The dried powder is supplied for this purpose in bottles of 5 and 30 gm. The long-continued use of nasal insufflations with posterior pituitary powder might cause chronic rhinopharyngitis.

The dosage is dependent upon the severity of the symptoms of the disease. In mild cases 0.5 ml. every 2 or 3 days will suffice. In severe cases the dosage schedule may be increased to 1 ml. one to 3 times daily.

Progress has been made in prolonging the oliguric action. *Pitressin Tannate* has been prepared in oil. The vial must be well shaken before use. Pitressin Tannate is slowly absorbed upon intramuscular injection, and the action is of long duration. The pharmacologic response to a single injection of Pitressin Tannate will be continued for about 48 hours (Thorn and Stein, 1941).

One milliliter of Pitressin Tannate in oil contains five pressor units. In the management of diabetes insipidus 0.3 to 1 ml. of the preparation is administered intramuscularly every 36 to 48 hours. Green and January (1940) used 1 to 1.5 ml. of the tannate preparation without untoward side reactions in the management of patients with diabetes insipidus. They report, however, that 2 ml. brings about a "very disagreeable sense of uneasiness."

Thorn and Stein (1941) found that the tannate preparation controlled the polyuria and greatly diminished the excretion of sodium chloride. Their observation was that the maximal effect of any single dose did not occur until 2 days after injection.

Vasopressin therapy in diabetes insipidus controls the symptoms of the disease. It must be continued indefinitely. The advance in the technic of medication by the production of Pitressin Tannate renders the management of the disease easier from the viewpoint of the physician and more comfortable from the standpoint of the patient.

**Synthetic vasopressin.** Vasopressin, like oxytocin, has been prepared synthetically. Besides, there are several modifications of the molecule that possess vasopressin activity. The advantage of the synthetic compound stems from its purity and freedom from foreign protein and oxytocin. Spiegelman (1963) successfully treated a case of diabetes insipidus with *8-lysine vasopressin* nasal spray. The patient was allergic to the natural hormone. The nasal spray was well tolerated, controlled the polyuria, and increased the specific gravity of the urine from 1.001 to 1.010. This advance in the prolonged therapy of diabetes insipidus is indeed a welcome one.

**Other drugs in diabetes insipidus.** Aminopyrine has been used for short-term therapy in the disease (see page 462). Alexander and Gordon (1961) used the diuretic hydrochlorothiazide, 50 mg. twice daily, in the disease. The urine volume decreased to $\frac{1}{3}$ to $\frac{1}{2}$ of the control value of 15 to 18 L. daily. The mechanism of the action of the thiazides in diabetes insipidus remains obscure. Laragh *et al.* (1958) proposed the following concept. The thiazide inhibited the production of "free water" in the distal tubule which normally results from the reabsorption of sodium and accompanying anions. Thus a drug that diminishes "free water" for urinary excretion should prove valuable in diabetes insipidus. This seems to the authors an oversimplification of a process that is not understood. If the thiazides are used in the disease, hypokalemia may be provoked.

These are interesting observations, but the drug of choice remains vasopressin or its synthetic derivative 8-lysine vasopressin.

### TISSUE DEHYDRATION OF ADRENAL INSUFFICIENCY (ADDISON'S DISEASE)

The secretion of epinephrine by the medullary portion of the adrenal glands has been discussed (see page 537). The adrenal cortex has been found to elaborate a number of steroid hormones which are essential to life. Swingle and Pfiffner (1931) were the first to observe that adrenalectomized cats could be kept alive for long periods of time by the injection of an extract which they prepared from the adrenal glands. The immediate use of such extracts in the control of adrenal insufficiency suggested itself. One of the outstanding clinical manifestations of adrenal cortex insufficiency is Addison's disease.

**Addison's disease.** This is a comparatively rare disease despite the fact that it has received widespread biochemical, pharmacologic, and clinical attention. In 100,000 admissions to the Mayo Clinic only 16 cases of Addison's disease were encountered.

The primary lesion in Addison's disease is in the adrenal cortex. There is a progressive necrosis of the gland which in many cases results from a tuberculous infection. The symptoms of the disease are *melanin pigmentation of areas of the skin, asthenia, loss of weight, tissue dehydration, hypotension,* and *hypoglycemia.* The classic description of Addison is of interest: "The leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of color in the skin."

**Electrolyte and water balance.** One of the outstanding effects of cortical insufficiency is the production of electrolyte imbalance and tissue dehydration. Patients with Addison's disease, as a rule, eat less food and drink little water. However, in adrenalectomized rats the desire for sodium chloride is increased. Absorption from the gastrointestinal tract is also likely to be altered. The primary cause of tissue dehydration and hemoconcentration, however, is the lack of differentiation of the tubule reabsorption mechanism between sodium and potassium ions. Sodium chloride is excreted in great abundance. Water is eliminated with it. Potassium, which is ordinarily readily excreted by the tubules, is reabsorbed in large amounts, producing a sodium-potassium imbalance in the tissues. Muscle cramps (miner's cramps) result from sodium loss.

For detailed accounts of the mechanism of the other conditions of altered metabolism such as carbohydrate, fat, and nitrogen, the reader is referred to the many exhaustive treatises on the subject. A digest of the physiologic mechanism of the cortical secretions is given in the following paragraphs as a basis for therapy in Addison's disease.

**Cortical secretions.** The cortical hormones are secreted when the gland is activated by the secretion of the pituitary adrenotropic hormone or when it is injected. The adrenotropic hormone diminishes the cholesterol and ascorbic acid content of the adrenal cortex. When these are diminished, cortical secretion occurs concomitantly.

All conditions which provoke adrenal cortical secretion are associated with a diminution of the cholesterol and ascorbic acid content of the gland. This occurs when the hypophysis initiates the secretion.

The stimulation of the autonomic nervous system, especially the sympathetic division, with epinephrine release appears to be an important factor in activating the pituitary to secrete the adrenotropic hormone. The secretion is further controlled by the adrenal cortical hormone level of the blood (Long, 1947).

About 30 steroid substances have been isolated from the adrenal cortex. These have been obtained in crystalline forms. There remains after their separation an *amorphous fraction.* This fraction is active in producing the effect of the gland, and its constituents are water soluble. It appears that the activity of the amorphous fraction is due mainly to *aldosterone.* Adrenal cortical extract is official.

**Adrenal Cortex Injection, N.F.,** *is a sterile solution in alcohol and water for injection containing a mixture of the endocrine principles derived from the cortex of adrenal glands of healthy domestic animals used for food by man. Each ml. of adrenal cortex injection exhibits a biologic activity equivalent to that of 100 micrograms of U.S.P. Hydrocortisone Acetate Reference Standard. It contains a suitable antibacterial agent.* Although this extract formerly played an important role in the treatment of the crises of Addison's disease, it has been replaced largely by intravenous drip of 1 L. of 5 per cent dextrose in isotonic salt solution to which has been added 100 mg. of hydrocortisone sodium succinate. Cortisone acetate, 100 mg., is injected intramuscularly (Thorn *et al.*, 1958).

Among the steroids which have been isolated are the androgenic substances *androstenedione, androsterone,* and *17-hydroxyprogesterone.* The female sex hormones *estrone* and *progesterone* have been separated. In addition to the male and female hormonal steroids, there are at least 6 compounds which exert the physiologic effects of the adrenal cortex. They may be divided into 2 groups, depending upon their chemical structure and physiologic function. The substances which appear to be primarily concerned with mineral metabolism and water balance are in Series I; those which affect carbohydrate metabolism are in Series II.

*Series I: Mineralocorticoids*

1. 11-desoxy-17-hydroxycorticosterone (Compound S)
2. 11-desoxycorticosterone
3. Aldosterone (electrocortin)

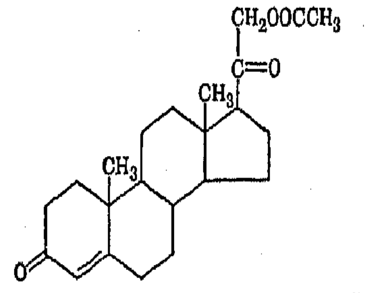
*Series II: Glucocorticoids*

1. Corticosterone
2. 17-hydroxy-11-dehydrocorticosterone (Compound E)
3. 11-dehydrocorticosterone (Compound A)
4. 17-hydroxycorticosterone (Compound F)

The second group of hormones does not materially affect mineral metabolism and water balance but promotes gluconeogenesis. Chemically the first group of hormones is characterized by the absence of an atom of oxygen in position "11." Aldosterone is an exception to this statement, having a hydroxyl group at position "11." It has also an aldehyde group at position "18." Like the glucocorticoids it also affects carbohydrate metabolism. The second group chemically contains an alcoholic or ketonic oxygen atom in position "11."

Compound E, or 17-hydroxy-11-dehydrocorticosterone, is the compound isolated and crystallized by Kendall, known as *cortisone.* The action of cortisone in various types of rheumatic disease is discussed on page 844.

Compound (2) of Series I, desoxycorticosterone, is readily synthesized from cholesterol. It is official in the form of its acetate. It is capable of restoring electrolyte balance, plasma volume, and blood pressure to normal patients with Addison's disease. The chemical constitution is shown in the formula below:



Desoxycorticosterone Acetate, U.S.P.

Cortisone (Compound E) is highly effective in controlling Addison's disease.

**Adrenal cortical hormones in Addison's disease.** In the foregoing paragraphs the symptoms of Addison's disease have been enumerated and the role of the cortical steroids in mineral and carbohydrate metabolism mentioned. The normal 17-ketosteroid excretion of men between 20 and 40 years of age is about 15 mg. daily. In normal women of the same age group the urinary excretion is about 10 mg. daily. In the male with Addison's disease the excretion drops to 1 to 6 mg. daily, which represents testicular output. In the female with Addison's disease there is practically no 17-ketosteroid excretion. The treatment of the disease is concerned primarily with the replacement of these steroids and thus the control of the symptoms resulting from their deficiency.

In the management of the acute deficiency in Addison's disease, rest in bed is of paramount importance. The electrolyte balance and the hypoglycemia are treated by normal salt solution and 5 per cent glucose intravenously. To the saline glucose infusion of 1000 ml. is added 1000 mg. of hydrocortisone sodium succinate. Intramuscularly, 100 mg. of cortisone acetate is given. If adequate response is not achieved, the hydrocortisone may be repeated once or twice in the first 24 hours. Serum electrolyte and hematocrit determinations should be done to guide the therapy. Ephedrine sulfate may be used also if the systolic blood pressure remains under 90 mm. If there is reason to suspect any associated infection, specific antibiotic therapy should be instituted.

In the routine management of the patient after the crisis is passed, the following measures are recommended: sodium chloride, 3 to 10 gm. daily in the form of enteric-coated tablets, is given. In very mild cases of Addison's disease salt alone may be sufficient for maintenance. As a rule, most patients require cortical hormones. Pellets of desoxycorticosterone acetate, 75 or 125 mg., may be implanted under the skin and are slowly absorbed from the fatty subcutaneous tissue. This procedure has been replaced by more dependable therapy. A newer long-acting desoxycortisone preparation is an aqueous suspension of *desoxycortisone trimethylacetate*. It is administered by deep intramuscular injection at intervals of 4 to 6 weeks. A single 30-mg. dose is estimated to provide 0.6 to 1 mg. daily from the injection site. In a large segment of patients with Addison's disease, Fluodrocortisone, a powerful sodium-retaining steroid, is used in oral doses of 0.1 mg. daily to maintain electrolyte balance. Given orally, 1 mg. of this agent is the equivalent of 25 mg. of desoxycortisone given by injection. The addition of cortisone, 12.5 to 25 mg. daily given orally, generally improves the patient's sense of well-being (Thorn *et al.*, 1958). Cortisone is a glucocorticoid and serves to maintain the normal carbohydrate metabolic pattern.

Edema usually appears in the patients undergoing desoxycorticosterone therapy. It may be reduced by diminution of the sodium chloride intake. The administration of potassium citrate may also be helpful until the edema subsides. Other symptoms, such as headache, hypertension, and cardiac enlargement, might result from excessive steroid therapy (Thorn, 1958).

*Aldosterone* appears to be the most effective agent in the treatment of Addison's disease. Mach *et al.* (1955) were able to maintain 2 patients with Addison's disease on 150 to 200 μg. of aldosterone daily. They estimate it to be 20 to 30 times more potent than desoxycorticosterone. Others also have confirmed this remarkable potency of aldosterone. It elicits no antirheumatic activity. However, in Addison's disease, at exceptionally low dosage levels, it appears to function adequately in correcting the mineral imbalance and the defect in carbohydrate metabolism. If this steroid becomes more abundantly available, it will undoubtedly play an important role in the treatment of this disease.

Prior to 1930, when no specific therapy for Addison's disease had been established, the 5-year mortality rate was about 96 per cent. Between 1930 and 1937, with a low potassium diet and salt therapy, this rate was reduced to about 76 per cent. With hormonal therapy the rate has further been reduced to about 50 per cent.

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# 52

# *Altering Renal Thresholds by Pharmacologic Agents*

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In the preceding chapter attention was directed to pharmacologic agents which produced a favorable shift in water balance when the latter was altered by disease. For the most part, this was accomplished by the use of diuretic and antidiuretic substances. Diuresis is achieved by lowering the renal threshold for such ionic constituents of the plasma as chloride, sodium, and potassium. Their excretion is accompanied by increased water excretion. The renal threshold can be lowered for such nonionic plasma constituents as glucose. This occurs in renal diabetes and can be achieved by the administration of phlorizin, a glycoside obtained from the bark of apple and certain other trees. It is obvious that this action is of no therapeutic value. However, the lowering of the plasma renal threshold for uric acid is of specific value in the treatment of gout.

### Alteration of the Renal Threshold for Uric Acid

**The nature of gout.** Gout is essentially a disease caused by a distortion of uric acid metabolism. It is a hereditary disease that was known to the ancient Greeks and Romans. The word "gout" is derived from the Latin "gutta" meaning drop; a drop in the joints. Sydenham, who suffered with gout, differentiated the disease from the other arthritides. In about the middle of the last century Garrod showed that gout was accompanied by *hyperuricemia.* Others later pointed out the relation of gout to faulty purine metabolism. The evidence extant that the incidence of gout is confined to those who eat and drink extravagantly is unconvincing. It may occur in plebeian individuals who through heredity carry the dominant gene responsible for hyperuricemia.

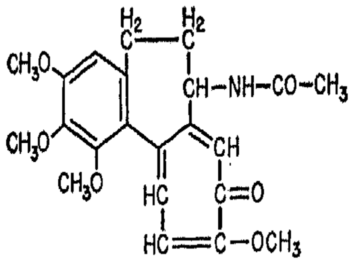
The disease likely owes its origin to an increased production of uric acid, a decreased rate of uric acid destruction, or a failure to excrete adequately uric acid. When uric acid with labeled $N^{15}$ is injected intravenously into normal subjects, the rate of formation of uric acid exceeds the rate of excretion by about 20 per cent. In gouty subjects the *uric acid pool* may increase to 15 times greater than the normal under the same experimental conditions. Benedict *et al.* (1952) showed that when $N^{15}$-labeled glycine is fed to gouty subjects, greater than normal amounts of $N^{15}$-labeled uric acid are excreted in the urine. This observation points to the conversion to uric acids in gouty subjects of such substances as glycines which ordinarily form urea. Wyngaarden (1957) suggested, after studies on the biosynthesis of uric acid, that it is possible that gouty individuals have developed a rapid "shunt biosynthesis" of uric acid which does not prevail in normal persons. However, conclusive proof of the "shunt mechanism" has not been established.

In addition to the distortion of uric acid metabolism, it is postulated that clinical gout has as a component an abnormal *adrenocortical androgen.* This controls the inherited hyperuricemia, which in turn is corrected by the steroid cortisone. In addition, patients with gouty diathesis exhibit an acute inflammatory response to uric acid deposits, which is relieved by ACTH. This is beneficial in many other types of allergic inflammatory responses. Hyperuricemia and urate deposits appear as the fundamental biochemical lesion manifested in gout. It follows, therefore, that (1) increased uric acid production, (2) decreased uric acid catabolism, and (3) faulty excretion of uric acid are the incriminating factors. Evidence indicates that in primary gout the increased rate of production of uric acid is the predominating factor. It appears that needle-sharp crystals of sodium urate deposited in the joints are responsible for the acute pain, against which an inflammatory reaction is established.

The problem of therapy in gout is set forth as follows: (1) suppression of the acute attack, (2) prevention and mobilization of urate deposits in the tissues, and (3) prophylactic measures which include preventing acute attacks and chronic joint disability. Our first consideration will be of the alkaloid colchicine in gout.

**Colchicine, U.S.P.** Colchicine is an alkaloid obtained from *Colchicum autumnale,* a small plant resembling the tulip and called *meadow saffron.* Colchicum was introduced as a medicinal agent in 1763 by Baron von Storch, physician to Empress Maria Theresa. Its empirical use was in "dropsical" conditions. Colchicine is present in the seed and corm to the extent of 0.3 to 0.9 per cent.

Colchicine occurs as pale yellow, amorphous scales or a powder. One gram of the alkaloid is soluble in 25 ml. of water. Unlike most other alkaloids, colchicine is not basic, and therefore does not combine with acids to form salts. The chemical constitution of colchicine is shown in the accompanying formula.



Colchicine, U.S.P.

The use of the alkaloid colchicine has largely replaced the galenical preparations of colchicum corm and seed. The wine and tincture of colchicum appear to be less reliable and more nauseating than a corresponding dose of colchicine.

**The use of colchicine in the treatment of gout.** Colchicine is often used diagnostically in gout. As a rule, gout or gouty arthritis will respond dramatically when the drug is administered. Other forms of arthralgias do not respond to the colchicine treatment. For this purpose 0.5 mg. of the drug is given every hour until the pain is relieved or diarrhea is produced. Then the drug is discontinued. Colchicine is also administered intravenously (0.65 mg.). It is claimed that often striking results are achieved by this method with a minimum of gastrointestinal distress. Suttenfield (1962) reviewed his experiences with intravenous colchicine over a 12-year period involving 3128 injections in 340 patients. He favored this method because (1) it provides more exact dosage; (2) it provides more prompt relief; (3) there is an absence of gastrointestinal symptoms, and (4) it obviates the necessity of giving opiates for the relief of pain.

In the control of the acute attack of gout, Bauer and Klemperer (1944) suggest 1 mg. of colchicine in the form of tablets every 1 to 3 hours day and night until the symptoms subside. If diarrhea ensues, 4 ml. of paregoric is administered to check the bowel movements and permit the continuation of therapy. As a rule, the symptoms are brought under control by 4 to 8 doses of the alkaloid. Colchicine is less effective in chronic gout than it is in the acute attack. Shanbrom and Rapoport (1958) found severe inflammatory lesions in the intestine of a patient who was subjected to an exploratory operation during colchicine therapy. There were hemorrhagic areas and ecchymoses. The picture resembled specific irritation of the bowel wall and its blood vessels owing to the absorption of some toxic, irritating agent.

Colchicine is also used prophylactically in gout. Regularly administered small doses of the alkaloid will frequently prevent the occurrence of attacks. Gutman and Yü (1952) suggest 0.5 to 1 mg. of colchicine every night or on alternate nights. Tolerance to colchicine does not develop and chronic toxicity to liver or bone marrow has not been experienced. Yü and Gutman (1961) followed for 5 years a series of 208 gouty patients on prophylactic colchicine therapy. The initial daily dose was 1 to 1.2 mg., which was maintained with most patients; in others the dose was reduced to 0.5 mg. Excellent results were achieved in 75 per cent of the patients: 22 per cent were satisfactory and the remainder unsatisfactory. Except for initial bowel hypersensitivity, no serious side effects were encountered. In a segment of the series, uricosuric agents were administered simultaneously with colchicine; this group experienced about the same degree of freedom from acute attacks as did those patients on colchicine alone. Thus, it is indicated that colchicine was responsible for the remission of the disease.

Walaszek *et al.* (1954) administered intravenously to man colchicine labeled with radioactive carbon $C^{14}$. Urinary excretion of $C^{14}$ occurred and accounted for from 70 to 97 per cent of the radioactive carbon given. Amounts varying from 4 to 47 per cent of colchicine were excreted unchanged in the urine.

Colchicine does not possess the capacity to mobilize urates. Therefore the administration of aspirin simultaneously with colchicine has been recommended.

**The mechanism of the action of colchicine.** No adequate explanation for the dramatic improvement in acute gout effected by colchicine has been offered. Denis (1915) found that the administration of colchicine neither increased the elimination of urates in urine nor diminished their concentration in the blood. As an analgesic, colchicine elicits no action on arthralgic pain. It has been suggested that the action of colchicine in gout is associated with its capacity to produce capillary dilatation. It is doubtful if this explanation is tenable. Colchicine also produces changes in the blood picture. First, there is a diminution of leukocytes and this is followed by a leukocytosis. This response resembles that of the injection of a nonspecific protein. We doubt, however, the association of this effect with the relief of gouty symptoms. One is forced to the conclusion that the action of the drug in gout rests entirely upon an empirical basis.

In studies with uric acid labeled $N^{15}$, colchicine was found to decrease the turnover rate of uric acid; in one case of gout there was a concomitant decrease in the size of the uric acid pool. It has therefore been suggested that colchicine may serve to diminish the rate of uric acid synthesis. This possible mechanism of the action of colchicine in gout, however, has not been definitely established.

Ferguson (1952) studied the pharmacologic responses elicited by colchicine in various laboratory animals. Not any of the responses to the alkaloid appeared to reveal the mechanism of its action in relieving gout. It was observed that the gastrointestinal effects are neurogenic in origin. Colchicine was found to elevate the blood pressure owing to arterial constriction induced by medullary stimulation. Colchicine also potentiates the excitatory effects of sympathomimetic drugs on the circulation.

Mugler and Gazet DuChatelier (1957) studied the mechanism of the action of colchicine in the treatment of gout. Their studies indicate that large doses of colchicine stimulate the activity of the adrenal cortex. For example, 3 mg. of colchicine given intravenously increased the urinary excretion of dehydroandosterone on the average of 30 per cent. They confirmed the potentiation of the effects of epinephrine previously reported by Ferguson (1952). In addition, they observed an anticholinergic effect of colchicine. They contend this action is associated with peripheral vasoconstriction, reduction of edema owing to increase in capillary resistance, and reduction of sensitivity to pain. Colchicine has been shown to chelate metal ions. The tropolone configuration of the third ring appears to be responsible for this action. It is possible that this property of the alkaloid is in some way associated with its beneficial effect in gout (Wallace *et al.*, 1962).

Although these observations are interesting, it appears that the specific mechanism of the action of colchicine in the acute phase of gout is still obscure.

**Colchicine poisoning.** The symptoms of colchicine poisoning involve first a *burning sensation* of the *throat* and *fundus* of the *stomach.* Severe *tenesmus* and *diarrhea* occur. The stools become bloody, and the severe gastrointestinal syndrome resembles that of arsenic poisoning or cholera. Death occurs through exhaustion from the gastrointestinal effects or through respiratory arrest. The fatal dose of colchicine has been estimated at 8 mg.

The treatment of the poisoning is largely symptomatic. Gastric lavage and strong tea (tannins) are indicated. Induced emesis may be helpful in removing the drug from the stomach. The administration of opium and belladonna preparations is valuable in relieving the severe tenesmus and tranquilizing the gut.

**Mitogenetic activity of colchicine.** Brués and Cohen (1936) observed that colchicine arrested cellular activity in metaphase. It is of special interest that this activity of colchicine obtains for vegetable as well as anima lcells. The effect of colchicine and many of its derivatives has been the subject of extensive investigation in the field of cellular physiology. Eigsti and Dustin (1955) reviewed the work. They summarized their findings in the following statements. The activity of the alkaloid was diminished by increasing the distance between the esterified side chains of rings B and C as in isocolchicine. At least one of the three methoxy groups of ring A is essential for activity. The amino group of ring B could be free or esterified. The C ring was most active when 7-membered and could have the methoxy group replaced by an amino group or a substituted amino group, but not by a hydroxyl group. For example, N-methylcolchicamide was found to elicit 4 times the activity of colchicine in arresting mitoses in cultivated chick embryo fibroblasts.

This fascinating field of study is pursued with great enthusiasm. Although at present its application to the treatment of human cancer has not proved successful, this approach is basic and worthy of exhaustive study.

**Desacetylmethylcolchicine (Demecolcin).** This compound differs chemically from colchicine in that a methyl group replaces the acetyl group at the N position in the molecule of colchicine. This substance was isolated from colchicum by Schär *et al.* (1954). Colsky *et al.* (1955) used Demecolcin in 10 patients with gouty arthritis. They obtained striking relief without the gastrointestinal distress which usually accompanies colchicine therapy. One patient, however, experienced a transient maculopapular rash. Most patients received an initial dose of 5 mg. and then 1 mg. of Demecolcin hourly for 3 doses.

Colsky *et al.* (1957) used Demecolcin in 26 patients with acute gouty arthritis. The results were satisfactory in 18 cases. Mild nausea occurred in 2 patients and 2 had mild diarrhea. In 2 cases of prolonged treatment with Demecolcine, pancytopenia developed along with a generalized loss of hair. The blood picture and growth of hair returned to normal after the therapy was discontinued. Thus, it appears that this additional alkaloid from colchicum is capable of producing gastrointestinal distress and owing to its bone marrow-depressing action one is enjoined not to use it as maintenance therapy. Its place appears to be in the suppression of acute attacks, for diagnostic purposes in gout, and for those persons who cannot tolerate colchicine.

**Gout, steroid metabolism and ACTH.** Clinical gout seems to be associated with a steroid metabolic disturbance. The gouty diathesis is believed to depend upon an abnormal adrenocortical androgen which controls the appearance of inherited *hyperuricemia.* The 11-oxysteroids and the adrenalcorticotropic hormone (ACTH) antagonize the effect of the abnormal androgen on urate metabolism. Furthermore, in clinical gout there appears to be an impaired capacity to respond promptly to 11-oxysteroid lack by increasing the 11-oxysteroid production. If the deficiency is permitted to persist, acute gouty arthritis may be precipitated.

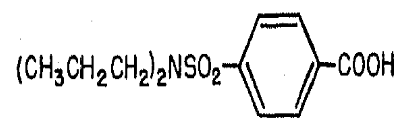
The intimate association of clinical gout with steroid metabolism promptly suggested the use of ACTH and cortisone in this condition. Wolfson *et al.* (1950) have used both agents in the management of gout. It was observed that the administration of ACTH will dramatically terminate an attack of gout. This occurs whether the attack is spontaneous or whether it has been induced by producing a state of 11-oxysteroid lack following the administration and withdrawal of ACTH. The attacks of gout are not permanently suppressed by the use of ACTH. They generally occur again after the withdrawal of the hormone.

Wolfson *et al.* (1950) showed that colchicine exhibited a marked inhibitory effect upon the occurrence of gouty attacks upon the withdrawal of ACTH. They used combined colchicine and ACTH therapy in 20 patients with gouty arthritis. This therapy proved to be the most rapid and effective in the management of those acute episodes. In almost all of the cases less than 100 mg. of ACTH was required.

It appears that the administration of colchicine elicits the release of small quantities of ACTH in man. However, the amount released is minute and the period evanescent. Therefore, it is unlikely that the release of ACTH by the presence of colchicine in the blood offers an adequate hypothesis for its prophylactic value in gout.

The principal use of ACTH in gout is to terminate established attacks of acute arthritis. For this purpose it is a dependable agent. In addition, ACTH may be considered a useful agent in acute gout which has failed to respond to colchicine. ACTH appears to be more dependable than cortisone or other adrenocortical steroids. ACTH is known to elicit *anti-inflammatory activity* and *increase the excretion of uric acid.* It is upon these 2 components of its action that its principal value in gout depends. The increased excretion of urinary dehydroandosterone observed by Mugler and Gazet DuChatelier (1957) upon the administration of colchicine, lends further evidence to the association of the action of the drug with the adrenal steroids.

**Probenecid, U.S.P. (Benemid) in gout.** Probenecid is *p*-(dipropylsulfanyl)-benzoic acid, as shown in the accompanying formula.



Probenecid, U.S.P. (Benemid)

Probenecid is a white, odorless, crystalline powder which is insoluble in water.

Probenecid acts at an enzymic level upon the tubular excretion of certain compounds. For example, it inhibits the renal tubular excretion of penicillin, *p*-aminosalicylic acid, and phenolsulfonphthalein. It was used to prolong the period for effective blood levels in penicillin therapy.

Man and the Dalmatian coach hound are unique among the mammals inasmuch as they each excrete considerable quantities of uric acid in the urine. Man reabsorbs through the tubules much of the uric acid in the glomerular filtrate. The Dalmatian coach hound, on the other hand, eliminates the acid by tubule secretion. Probenecid inhibits the tubule resorption of uric acid in man and in the Dalmatian coach hound inhibits the tubule secretion of the acid (Beyer *et al.*, 1951).

Probenecid is used in the treatment of chronic gout as a *uricosuric* agent. A single dose of 2 gm. causes a rapid increase in urinary uric acid excretion. This is due to the highly selective action of probenecid in suppressing the tubular reabsorption of urate. Talbott (1951) observed the uric acid pool of a gouty individual to be 2500 mg. Upon the intravenous administration of uric acid labeled $N^{15}$ this increased to 4000 mg. Upon the administration of probenecid the uric acid pool was rapidly reduced to a normal value of 1500 mg. Generally, normal serum urate values can be achieved within one week when probenecid is administered in gout. By continued dosage at a reduced level these may be maintained indefinitely. For this purpose probenecid is superior to salicylates. The 2 drugs should not be used concurrently since their effectiveness in promoting the excretion of uric acid is mutually antagonistic.

Crone and Lassen (1955) observed that probenecid administered to patients with unaltered purine metabolism caused a marked excretion of uric acid, but the plasma levels remained unchanged for a few days. They contend that the progressive rise in uric acid excretion cannot be attributed to a continuous depletion of the uric acid from the organism. They are of the opinion that "an increased uric acid production must have been effected either by the direct action of probenecid on the tissues or by the lowered plasma uric acid level." In most of their experiments the increased uric acid excretion stopped on the first day after the discontinuance of probenecid. Increased plasma levels persisted for several days, however, which they suggest was due to increased uric acid production. It is unlikely that this is caused by the action of probenecid on the tissues as it persists after the action of the drug on the kidneys has ceased. It appears to us that this observation is one of a compensatory or rebound type of mechanism responding to an abrupt uric acid excretion.

Probenecid elicits no analgesic action. It furthermore is of no value in reducing inflammation other than that associated with increased uric acid excretion. The optimal daily dose of probenecid is 1 to 2 gm. As a precautionary measure the dose should be kept minimal. Allergic responses to the drug have been recorded (Gutman and Yü, 1952). If the patient has a history of urinary urate calculi, or the uricosuric response is very marked, the drug must be given at a smaller dosage level. In these cases sodium bicarbonate should be administered to alkalinize the urine. Also a high fluid intake is desirable. Occasionally, when probenecid is administered in chronic gout, acute symptoms of the disease may occur at first. These, however, are transient. Nausea and anorexia are encountered with probenecid therapy in some individuals. To our knowledge there have been no cases of blood dyscrasias reported.

Probenecid is useful also in the treatment of recurrent renal calculi which are composed of uric acid. Bernstein *et al.* (1958) reported success in the treatment of this condition when other measures such as urine alkalinization and salicylate therapy had failed.

**Sulfinpyrazone (Anturane).** Anturane is a newer uricosuric agent, which like probenecid decreases the renal tubular reabsorption of uric acid. Chemically, Anturane is a 1,2-diphenyl-4-(2′-phenylsulfinylethyl)-3,5-pyrazolidinedione. It is a white powder which is sparingly soluble in water.

Anturane, like probenicid, is not recommended in combination with salicylate therapy as the drugs antagonize each other. Because of the rapid excretion of uric acid with Anturane therapy, the fluid intake should be increased and alkalinizing salts given to prevent urolithiasis.

The rapid mobilization of uric acid sometimes precipitates an acute attack of gouty arthritis in the initial stages of therapy. Colchicine may be administered concomitantly to relieve the patient. Gastrointestinal distress is the most frequent side effect. Anturane is interdicted in ulcer patients. Although leukopenia and thrombocytopenia have been reported in only 1 patient receiving Anturane, the possibility of blood dyscrasias arising from its use should be considered.

Anturane is readily absorbed from the gastrointestinal tract and excreted by the kidneys in the urine similar to probenecid. Its potency as a uricosuric agent is 4 to 6 times greater than that of probenecid. Certain gouty patients who have shown refractoriness to other uricosuric agents have responded favorably to Anturane. Anturane is available in 100 mg. scored tablets. Maintenance dosage in gout range from 400 to 800 mg. daily in divided doses.

**Other drugs in gout.** Nicolaier and Dohrn (1908) introduced cinchophen, N.F. (Atophan) in the treatment of gout. It is 2-phenylquinoline-4-carboxylic acid. It elicits analgesia and increases the urinary excretion of uric acid. Owing to gastrointestinal irritation produced by the drug and occasional cases of *fatal hepatitis*, its use was abandoned. The incrimination of cinchophen in producing hepatitis rests on an insecure basis. An American Medical Association Journal editorial (1947) stated that the atrophy of the liver erroneously attributed to cinchophen therapy was, in fact, infectious hepatitis.

Neocinchophen, N.F., replaced cinchophen for many years in the treatment of gout. It is less irritating to the gastrointestinal tract. Neocinchophen, which is 2-phenyl-4-carbethoxy-6-methylquinoline, like its precursor cinchophen, has likewise been nearly discarded in the treatment of gout.

Kuzell *et al.* (1952) used Butazolidin, p. 845, in the treatment of gout. Complete remission of symptoms in acute gout was experienced by most of the patients. The effect was very prompt. The toxicity of this drug is a limiting factor of use in the routine treatment of gout.

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# 53

# *Metabolic Effects of the Adrenal Corticotropic Hormone and Adrenocortical Steroids and Treatment of the Arthritides*

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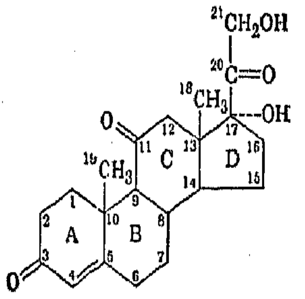
In the chapter on water balance the effect of the adrenocortical hormones on water balance and mineral metabolism was considered in the treatment of Addison's disease. In this chapter the profound metabolic effects of these hormones on metabolism and their application in the treatment of various diseases will be discussed. Since these agents and their synthetic derivatives are used in the treatment of rheumatic disease, the use of these and other drugs in the treatment of this prevalent disease will be considered.

## Adrenal Corticotropic Hormone (ACTH) and Adrenocortical Steroids

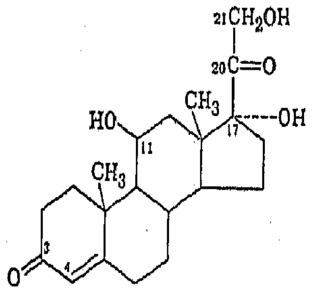
**Historical development of ACTH and cortisone.** The scientific staff of Armour and Company of Chicago, applying the methods developed by H. C. Li at the University of California, extracted ACTH from the pituitary glands of hogs. In 1946, John R. Mote of the Armour Company made available to the medical profession a small amount of the hormone for trial.

Thorn *et al.* (1949) at Harvard were the first to study ACTH in a variety of clinical conditions and to assess its physiologic function in man. They observed that ACTH was capable of causing a remission of the symptoms of *rheumatoid arthritis*, *rheumatic fever*, *lupus erythematosus* and *gout*. Thorn's studies were carried out with ACTH (Armour Standard). The Armour Standard is of such potency that 4 μg. given intravenously to a hypophysectomized rat will lead to a fall in adrenal ascorbic acid of 20 to 40 per cent. The fall in the circulating eosinophils affords the most sensitive index to the activation of the adrenal cortex. This effect usually becomes manifest before the others are observed.

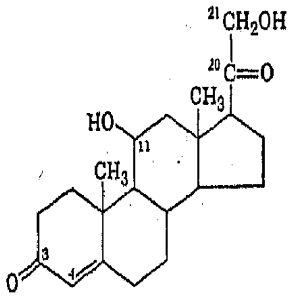
The discoverer of cortisone is Edward C. Kendall of the Mayo Foundation for Medical Education and Research, page 833. In 1935, Kendall had isolated a few granules of Cortisone from cortical extracts. It was called Kendall's Compound E. The substance was shown to have a marked effect on muscular activity in laboratory animals. Compound E increased the ability of the animal to resist exposure to cold and poisons and induced physiologic stresses. The supply was too meager for human trial. The method of preparation was tedious and did not give promise of producing an adequate supply of Compound E. The structure of cortisone and its relationship to the other natural and synthetic steroids of medical interest are shown in the following formulas:



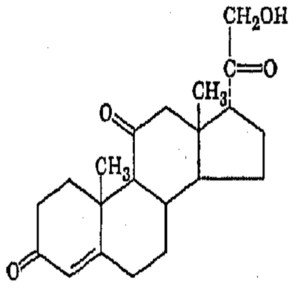
Cortisone
(Compound E)



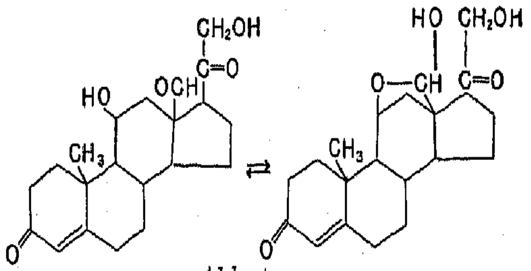
Hydrocortisone
(Compound F)



Corticosterone
(Compound B)

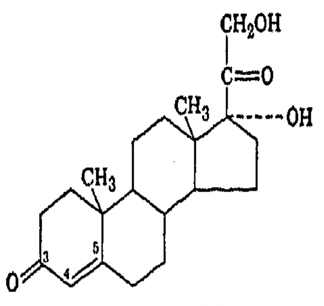


11-dehydrocorticosterone
(Compound A)

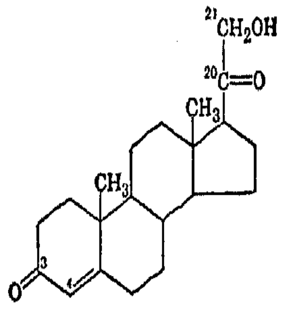


Aldosterone

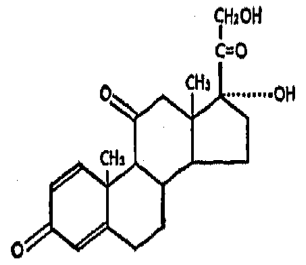
It will be observed that the 3 steroids are glucocorticoids, page 817. They have an oxygen linkage at the same position, namely, "11." Kendall achieved the partial synthesis of Compound E. It was rumored in 1941 that the pilots of the *Luftwaffe* were being injected with certain cortical hormones which enabled them to withstand extra-



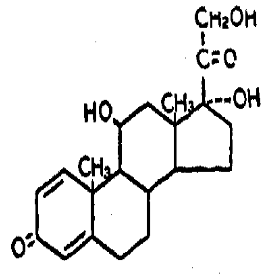
Compound S



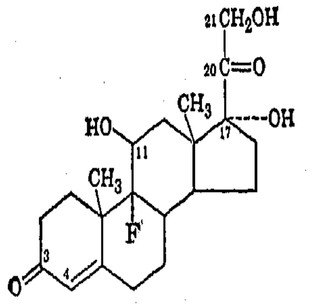
Desoxycorticosterone



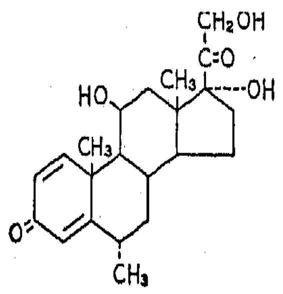
Δ¹-Cortisone
(Prednisone)



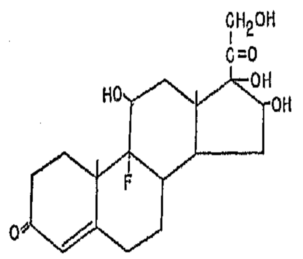
Δ¹-Hydrocortisone
(Prednisolone)



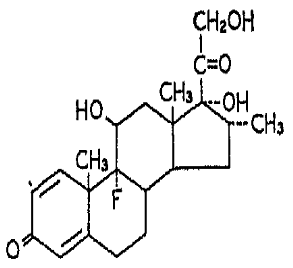
9α-Fluorohydrocortisone



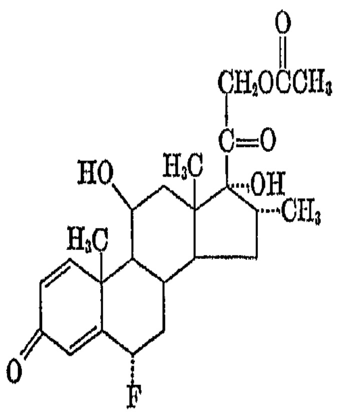
6α-Methylprednisolone
Medrol



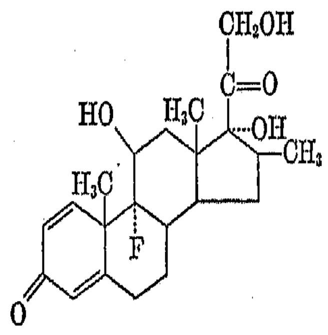
Aristocort, Kenacort
9α-fluoro-16α-hydroxyprednisolone



Dexamethasone
9α-fluoro-16α-methylprednisolone
Decadron, Gammacorten, Deronil



Paramethasone Acetate, Haldrone
6α-fluoro-16α-methylprednisolone
21-acetate



Betamethasone, Celestone
9α-fluoro-16-β-methylprednisolone

ordinary stress. The synthesis of the cortical hormones then became an emergency problem.

The Mayo group, in collaboration with the scientific division of Merck and Company, achieved the synthesis of Compound A from one of the bile acids. Its action was disappointing. It was not useful in the control of Addison's disease.

Early in 1946 Sarett of the Merck laboratories produced a partial synthesis of Compound E. In May, 1948, the 37 steps in the synthesis were achieved. By September of 1948, Compound E, then named cortisone, was synthesized in grams instead of milligrams.

About this same time Hench of the Mayo Clinic observed that women suffering from rheumatoid arthritis experienced a remission of their symptoms during pregnancy. He recalled that he and other observers had noted a reversibility of the rheumatoid process in hepatitis and jaundice. Since the bile acids contain chemical nuclei of a steroidal nature similar to those of the adrenal cortical hormones, the relation of rheumatoid arthritis to functional disturbances of the adrenal cortex was suggested. This led to the first clinical trial of cortisone with its now familiar dramatic results.

In September, 1948, Hench tried his initial case of rheumatoid arthritis with the newly available cortisone. The results were dramatic.

**Physiologic effects of ACTH.** It appears that the primary function of ACTH is that of *stimulation of the secretions of the adrenal cortex.* These effects have been exhaustively studied and may be summarized into the following classifications. It has already been mentioned that the injection of ACTH elicits a prompt hematologic response. This is characterized by a *fall* in the *total eosinophil count* of about 75 per cent. There is a *drop in lymphocytes* and *increase of neutrophiles.* Metabolic changes which are initiated are prompt in making their appearance. These include an *increased urinary excretion of uric acid, 17-ketosteroids,* and *potassium.* The *blood sugar level* is slightly *elevated* and there is a small *increase* in *liver glycogen storage. Sodium excretion* in the urine is *diminished* and a slight *increase* in *body weight* is experienced. Blood pressure appears to be essentially unaffected by ACTH. The serum globulin content was unaffected, and no increase in antibody concentration was observable.

These metabolic changes suggest that exogenous ACTH initiates the secretion of the adrenal cortical steroids. These include *hydrocortisone, cortisone, corticosterone,* and *aldosterone,* page 829. ACTH increases the rate of hydrocortisone secretion to the greatest extent, corticosterone to a lesser extent, and likely causes no significant increase in aldosterone secretion.

As the primary effect of ACTH is upon the adrenal cortex, one might expect profound changes to occur in this structure. The changes are both morphologic and biochemical. The predominant morphologic change is *hypertrophy.* The biochemical changes are mainly associated with *cholesterol and ascorbic acid metabolism.* The administration of a single dose of ACTH will cause *a drop of 50 per cent in the cholesterol content* of the gland of the rat within a period of 3 hours. The diminution of cholesterol content of the gland is concomitant with increased cortical steroid activity. The *ascorbic acid content* of the gland likewise *decreases* upon the injection of ACTH. This response is so sensitive that it may be used as a bioassay for ACTH activity. The biochemical relationship between ascorbic acid and the cortical steroids has not been established.

Sayers *et al.* (1948) developed the ascorbic acid assay for ACTH activity. This potency test became the basis for the standardization of ACTH. The activity of 1 mg. of a standard preparation was defined as an international unit. When adopted by the United States Pharmacopeia the international unit was by definition made the U.S.P. unit.

The U.S.P. recognizes ACTH as *corticotropin injection.* It is a "sterile preparation of the principle or principles derived from the anterior lobe of the pituitary gland of mammals used for food by man, which exert a tropic influence on the adrenal cortex. It possesses a potency of not less than 80 per cent and not more than 125 per cent of that stated on the label in U.S.P. Corticotropin Units. It may contain a suitable antibacterial agent."

This injection is intended for intramuscular or subcutaneous administration unless the label indicates it is for intravenous use.

The U. S. P. also recognizes a *repository corticotropin injection* which contains a vehicle to prolong its therapeutic action. The vehicle usually contains gelatin and is called ACTH Gel.

There is available a *corticotropin purified* which has the advantage of producing fewer sensitization reactions than corticotropin. One unit of the purified product produces the same clinical effect as 3 or 4 units of corticotropin. For convenience the potency of corticotropin purified is expressed in activity equivalents to a specified number of U.S.P. units of corticotropin, so that they may be used interchangeably without dosage adjustment.

**Corticotropin-zinc Hydroxide Suspension, U.S.P.** is a preparation of purified corticotropin adsorbed on zinc hydroxide which delays absorption from the site of injection. Hence the duration of action is prolonged. The preparation is a suspension for injection containing 200 units of corticotropin and 10 mg. of zinc in 5 ml.

For purposes of comparison it is estimated that 25 U.S.P. units of ACTH Gel are the approximate equivalent of 100 mg. of cortisone, or 50 to 75 mg. of hydrocortisone, or 25 mg. of prednisone or prednisolone.

**The nature of ACTH.** The investigators of the Armour Laboratories reported the isolation of pure ACTH. It is a protein with a single chain of amino acids. It is a white powder soluble in water. The molecular weight is about 3500. This value is less than was formerly supposed.

Li and his associates (1955) determined the complete molecular structure of ACTH. From sheep ACTH Li has identified the 39 amino acids in the straight chain molecule. The molecule was subjected to degradation, breaking off 11 amino acids on the right side of the chain. The residue with 28 amino acids (molecular weight 3000) retained the full physiologic activity of the larger molecule (150 units/mg.). They are uncertain as to whether or not further degradation is possible without loss of activity.

The same team of investigators has succeeded in synthesizing short forms of the ACTH molecule, some of which were shown to evoke highly specific biologic effects. For example, in 1960 a molecule with high ACTH potency was synthesized with 19 amino acids. Two years later Li *et al.* synthesized a compound ACTH-like in character containing 19 amino acids. The most striking effect of the compound was its lipolytic effect, which exceeded that of the natural hormone.

The determination of the structure of ACTH and the synthesis of short forms of the molecule is a splendid contribution to our understanding of the activity of protein hormones. Furthermore, it bespeaks the synthesis of shorter amino acid chain ACTH-like molecules with highly specific biological activity for therapeutic use.

**Therapeutic uses of ACTH.** The main groups of diseases in which ACTH is indicated are: (1) *rheumatic diseases*, (2) *skin diseases*, (3) *ocular diseases*, and (4) *allergic manifestations*. The first classification includes *rheumatoid arthritis*, *rheumatic fever*, *gout*, and other *rheumatic states* in which the hormone generally yields good results. The second group includes many skin conditions such as *lupus erythematosus*, *disseminated pemphigus*, *angioneurotic edema*, *acute urticaria*, *leukemia*, and others. In these, ACTH therapy has been for the most part successful. The third category embraces *ocular burns*, *iritis*, *uveitis*, *corneal ulcers*, and other *ocular diseases*. ACTH has proved useful in the treatment and cure of these conditions. The fourth group includes *bronchial asthma*, *allergic rhinitis*, and *intractable hay fever*. The hormone affords good results in these conditions.

ACTH usually brings about a remission of many chronic diseases such as arthritis and gout. Generally, after the discontinuance of therapy a recurrence of the disease takes place. In self-limiting acute conditions such as acute urticaria and angioneurotic edema the results are dramatic and permanent after therapy has been discontinued.

ACTH is usually administered intramuscularly or subcutaneously. It may be given intravenously. ACTH is not effective orally or when applied locally to inflamed tissue. Its value as a therapeutic agent depends upon the integrity of the adrenal glands of the patient to whom it is given. If through disease the glands are incapable of undergoing stimulation, ACTH will be of no value. Generally, ACTH is given in doses of 10 to 15 units every 6 hours. If the desired results are not obtained within several days the dose may be increased to 20 or 25 units every 6 hours. Once results are achieved the dosage schedule is diminished by omitting dosage periods and reducing the unitage for maintenance.

The intramuscular injection of corticotropin solution reaches its maximal effect in 4 hours. It has little action after 8 hours. The gelatin preparations exhibit their maximal effect in 8 to 12 hours, and 85 per cent of their activity occurs during the first 24 hours after administration. Meyers and Wolfson (1955) approximate that It is estimated that 80 units of corticotropin gel given once every 24 hours is the equivalent of 33 units of corticotropin given every 12 hours, or 20 units every 8 hours, or 10 units every 6 hours. The advantage of the gel dosage form is apparent.

**Mechanism of action of ACTH.** The mechanism of action by which ACTH causes a stimulation of the release of corticosteroids has been the subject of extensive investigations. Recent studies serve to elucidate the mode of action. Haynes and Berthet (1957) established that ACTH increased markedly the phosphorylase activity in adrenal tissue. Haynes (1958) produced evidence to indicate that ACTH produced an accumulation of adenosine-3′,5′-monophosphate in adrenal cortical tissue. This agent presumably causes the activation of phosphorylase. The greater activity of this enzyme permits glycogen to be more rapidly depolymerized and converted to glucose-1-phosphate. This ester is converted rapidly into glucose-6-phosphate which is metabolized principally by the dehydrogenase system. Through the activity of the dehydrogenase system, reduced triphosphopyridine nucleotide is produced. This, it is proposed, provides the energy for the necessary steps in the synthesis of corticosteroids. From their stores in cortical tissue they pass into the circulation. Adding support to this interesting hypothesis is the work of Koritz *et al.* (1958) who showed that the addition of glucose-6-phosphate and TPN to rat adrenal slices augmented the production of corticosteroids by the tissue.

**The fate of ACTH.** Complete knowledge of the metabolic fate of ACTH is not available. When injected intravenously the hormone rapidly disappears from the circulation. The plasma level falls in a logarithmic pattern. Its half-life is about 6 minutes. The rapid disappearance of injected ACTH may be due to inactivation or catabolism, distribution, and tissue fixation or excretion. It appears that certain body tissues can rapidly fix ACTH.

**Contraindications of ACTH.** There are certain conditions in which the administration of ACTH is definitely contraindicated. For example, it might cause the further spread of *tuberculosis*. In *azotemic nephritis* the nonprotein nitrogen of the blood might increase. *Acute psychoses* might be aggravated. *Cushing's syndrome* is definitely worsened, and *active peptic ulcers* might be made to perforate. In *congestive heart failure* and *hypertension* the retention of sodium caused by ACTH requires careful attention. In *diabetes* insulin requirements might be increased if ACTH is administered.

**Untoward effects of ACTH.** From what has been said regarding the physiologic function of ACTH, it is apparent that this hormone exerts a profound effect upon many of the somatic metabolic processes. Hench *et al.* (1950) have made a comprehensive study of some of the side effects produced in individuals to whom ACTH had been administered in the treatment of rheumatoid arthritis and other conditions. The untoward effects appear to bear a direct relationship to the size of the dose and the period over which it is administered. The following symptoms have been noted by the Mayo Clinic investigators: *rounding of the facial contour*, *mild hirsutism*, *acne*, *keratosis pilaris*, *muscular weakness*, *edema*, *amenorrhea*, *purplish cutaneous striations*, *impairment of carbohydrate tolerance*, *negative nitrogen balance*, *and hypochloremic*, *hypopotassemic alkalosis*.

It is clear that the action of ACTH is mediated through its stimulation of the function of the adrenal cortex. It has been suggested that this exogenous stimulation of the adrenal cortex suppresses pituitary corticotropin secretion. Clinical and experimental evidence indicates that while exogenous corticotropin may inhibit pituitary release of ACTH temporarily, it causes an increase in pituitary concentration of ACTH (Kitay *et al.*, 1958).

These effects clearly indicate the precautions and vigilance that must be enjoined in the use of ACTH in any condition. Indeed, the administration of ACTH in most conditions in which it is indicated must be considered from the point of view of the physiologic well-being of the patient, as well as the control of the immediate disease entity.

**The physiologic effects of cortisone.** More than 40 steroids have been isolated from the adrenal cortex; there are perhaps others which will be isolated and characterized chemically (Peterson, 1959). In man, *hydrocortisone* is the principal glucocorticoid secreted. It is also likely that *aldosterone* is the principal mineralocorticoid secreted by the adrenal cortex of man. Corticosterone is also secreted in small quantities. Cortisone was the first adrenal cortical hormone synthesized and used in clinical medicine. It was thought that it was the natural glucocorticoid of the adrenal cortex. Later investigations revealed that the principal glucocorticoid secreted by the adrenal cortex is hydrocortisone. Qualitatively, their functions are the same; quantitatively, hydrocortisone is more potent Although in therapy many synthetic derivatives of cortisone have advantageously replaced it, the activity of these agents qualitatively follows the pattern of that of cortisone.

Cortisone is one of the adrenal cortical hormones. Its structure is shown on page 829. Unlike ACTH, therefore, when it is administered it does not stimulate the adrenal cortex. It serves in a measure as replacement therapy. The preceding statement requires certain qualifications. It is true that cortisone is a natural hormone of the adrenal cortex. But it has never been established that insufficient amounts of it in the circulation are responsible for the arthritides and other conditions in which cortisone is effective. Indeed, the plethora of cortisone administered in treatment must be considered as a drug. The case is analogous to the treatment of the asthmatic spasm with the hormone epinephrine, but not complete replacement therapy similar to the use of insulin in diabetes. Its value, therefore, is not dependent upon the functional capacity of the adrenal cortex. The effect of ACTH is due in a large measure to its stimulation of the adrenal cortex to secrete hydrocortisone. Hydrocortisone and cortisone are glucocorticoids. Either produces a marked immediate *reduction of the eosinophil count, a lesser reduction in the lymphocyte count, and an increased total white cell count, owing to polymorphonuclear cells.* ACTH produces adrenal cortical hyperplasia with an increase of 17-ketosteroid and 17-hydroxysteroid excretion in the urine. Cortisone produces a decrease in the urinary excretion of 17-ketosteroids and 17-hydroxysteroids. Cortisone elicits a mild hyperglycemia. These effects singly or in their entirety offer no adequate explanation for the dramatic results achieved with cortisone in rheumatoid arthritis and other diseases.

Cortisone acetate is official in the Pharmacopeia. It is a white crystalline powder which is insoluble in water. The U.S.P. also recognizes tablets of cortisone acetate 5 and 25 mg. Also official is sterile suspension of cortisone acetate containing 25 mg. and 50 mg./ml. for intramuscular use and an ophthalmic suspension containing either 0.5 or 2.5 per cent of cortisone acetate. Cortisone acetate is available under the names *Cortone acetate* and *Cortogen acetate.*

**Absorption and fate of cortisone.** Cortisone is likely a precursor or metabolite of one of the principal adrenal cortex glucocorticoids. It is not found in the adrenal venous blood or the peripheral blood of animals. On the other hand, hydrocortisone is found in the circulating blood. When cortisone is injected intravenously into dogs, 90 per cent of the dose disappears within 10 minutes. Liver perfusion of cortisone solutions causes the rapid disappearance of the steroid. The urinary excretion of cortisone, if it occurs, is difficult to evaluate owing to the presence of various endogenous steroids.

Cortisone acetate is rapidly and apparently completely absorbed from the gastrointestinal tract. The oral dose on a weight basis is equivalent to the intramuscular dose, and frequently the effect is more rapid upon oral administration. In some instances 1½ times the intramuscular dose is required for equivalent oral activity.

**Therapeutic uses of cortisone.** Cortisone has been proved to be useful in the treatment of the same groups of diseases in which ACTH is used, page 832. It is available orally and is active upon local application to inflamed tissues.

In conditions in which cortisone is indicated it is given in the following manner. Four tablets, 25 mg. each, are given at intervals during a day for 4 or 5 days. When the inflammatory process is suppressed, the quantity of cortisone is reduced in a "step-like" manner, using half tablet dosage and increasing the interval between doses. The smallest dose that will control symptoms is considered the maintenance level. Small doses may be administered for long periods of time without untoward effects.

The reduction of salt intake and the administration of 1 to 4 gm. of potassium chloride daily are helpful in restoring electrolyte balance during cortisone therapy.

It should be emphasized at this point that several of the newer synthetic steroids offer therapeutic advantage over cortisone and are thus preferred in treatment. However, as stated previously, their action is qualitatively the same as that of the parent compound cortisone.

**Untoward effects of cortisone.** Cortisone elicits a profound effect upon many of the physiologic processes of the body. Many of the symptoms set forth on page 833 as untoward effects of ACTH have been observed to be produced by cortisone when administered in sufficient dosage for an ample period of time. Generally the appearance of the *"Cushing syndrome"* of *altered fat distribution, glycosuria,* and *hirsutism* is indicative of the *altered physiologic processes.* The effects of altered metabolism are sufficient to warrant *great caution* in the use of cortisone, as in the case of ACTH.

In addition to the foregoing side effects cortisone may produce mental changes of a varying degree. The physician should be especially cautious of this side effect on a high dosage schedule. For example, Taylor *et al.* (1950) treated 27 cases of advanced carcinoma with cortisone; euphoria occurred in 22, hypomania in 3, and frank schizoid reactions in 2.

**Hydrocortisone, U.S.P.** Hydrocortisone differs chemically from cortisone in that it contains a hydroxyl group at carbon atom "11" instead of the ketone group, page 829. It is a white or nearly white crystalline powder which is insoluble in water.

The therapeutic uses of hydrocortisone are identical with those of cortisone acetate. Hydrocortisone, when administered orally, is more effective than cortisone acetate. Hydrocortisone acetate is less effective than cortisone acetate owing to its low solubility in aqueous fluids and low rate of absorption. Even when administered intramuscularly, hydrocortisone acetate is very poorly absorbed from the injection site. Therefore, it is clear that hydrocortisone acetate is not available for acute states of adrenal insufficiency such as Addison's disease. On the other hand, hydrocortisone is more effective than cortisone acetate. As discussed previously, hydrocortisone appears to be the predominant glucocorticoid secreted by the adrenal cortex. For topical application in inflammatory states hydrocortisone acetate is especially valuable since it exerts the anti-inflammatory activity of hydrocortisone and is not readily removed from the site of application by absorption.

Like cortisone, hydrocortisone is metabolized by the liver. The ketonic group in ring "A" is reduced to a hydroxyl group and the side chain at position "17" undergoes degradation. Enzymic reduction of the double bond in the steroid ring readily occurs. Two groups of enzymes in liver homogenates are capable of carrying out the reduction: one of these in the soluble fraction produces the 5 $\beta$ isomer, and the others present in the microsomes catalyzes the formation of the 5 $\alpha$ isomer. It appears that TPNH controls the rate of steroid reduction in the liver (Tomkins, 1959).

Peterson and Wyngaarden (1955) used tagged hydrocortisone-4-$C^{14}$ and showed that over 90 per cent of the dose of hydrocortisone (oral or intravenous) is excreted in the urine within 72 hours. Less than 0.1 per cent is excreted unchanged.

The therapeutic use, side effects, and contraindications of hydrocortisone are the same as those of cortisone acetate. It appears from the reports of various investigators that the maintenance dose is about ⅔ that of cortisone acetate.

**Hydrocortisone Acetate U.S.P. (Hydrocortone Acetate).** Hydrocortisone acetate occurs as a white crystalline powder which is insoluble in water. The Pharmacopeia recognizes also a sterile aqueous suspension containing 25 mg./ml. in a suitable suspending medium. An ointment of hydrocortisone acetate in strengths of 0.5 to 2.5 per cent is also official. Hydrocortisone acetate is injected intra-articularly in the form of a suspension. It provides local relief at the affected joint without concomitant systemic effects. It therefore is especially valuable in rheumatoid arthritis when only 1 or 2 of the peripheral joints are affected. Clinical improvement may be seen in a joint from the injection of 25 mg. of hydrocortisone acetate. The duration may extend from 3 to 21 days. Hollander *et al.* (1951) used the steroid in 69 cases of rheumatoid arthritis. The results were uniformly good and repeated injections elicited further amelioration of the symptoms. Hollander (1953) reported on over 8000 injections into 852 patients. Relief was obtained within a few hours and persisted for 3 days to several weeks. The microcrystals disappear from the synovial fluid after about 2 hours following the injection. Hollander has injected the same joint 47 times in a period of 2 years. These findings have been confirmed by other observers (Stevenson *et al.*, 1952; Kersley and Desmarais, 1952; Scull, 1962).

**Prednisone U.S.P. and Prednisolone U.S.P.** These are 2 synthetic steroids. Chemically, prednisone is cortisone with an additional double bond between the carbon atoms "1" and "2" in ring "A." Prednisolone chemically is hydrocortisone with an additional double bond between carbon atoms "1" and "2" in ring "A," page 830. These 2 steroids have the same therapeutic indications as cortisone and hydrocortisone. The essential differences are: (1) they are 3 to 5 times more potent, and (2) they do not cause appreciable sodium retention or potassium excretion. Therefore the tendency to produce edema under medication with prednisone or prednisolone is less than with cortisone or hydrocortisone.

Pechet *et al.* (1959) compared the metabolic features of prednisone and prednisolone with cortisone in Addisonian patients. Prednisone and prednisolone 30 mg. daily resulted in slight sodium loss, whereas 150 mg. of cortisone daily caused marked sodium retention. Endogenous creatinine clearance was markedly raised with prednisone and prednisolone, and unaffected by cortisone. Transitory potassium diuresis on starting therapy and retention on stopping were less marked with prednisone and prednisolone than with cortisone. Nitrogen loss was elicited by 30 mg. daily doses of prednisone. Both steroids depressed the excretion of 17-ketosteroids. Fifty milligrams of prednisone effected a 3-fold increase in blood-corticoid levels which persisted for 6 hours after the oral dose. Thorn (1955) observed that these synthetic steroids cause greater increase in urinary nitrogen excretion.

Since the publication of the first paper on the use of prednisone and prednisolone in the treatment of rheumatoid arthritis by Bunim *et al.* (1955) many reports have appeared confirming the value of these steroids. They appear to replace adequately and with advantage cortisone and hydrocortisone in *rheumatoid arthritis* and *allied conditions*, *bronchial asthma* and *various inflammatory ocular diseases*, *dermatoses*, and *allergic disorders*. In Addison's disease it is obvious that the failure of prednisone and prednisolone to cause sodium retention, would render these steroids less effective than desoxycorticosterone and cortisone.

The side effects of prednisone and prednisolone recorded have been mild for the most part. *Insomnia* and *gastric distress* are most frequently encountered. The activation of dormant duodenal and gastric ulcers may occur. To avoid this the agents are now available in double tablets containing the gastric antacids aluminum hydroxide and magnesium trisilicate. Mild hirsutism has occurred, and rounding of the face is occasionally encountered. It does appear that the administration of prednisone and prednisolone provide a much safer regimen of therapy than do cortisone or hydrocortisone especially for prolonged use.

Prednisone is available under the names *Delta-Cortef*, *Deltra*, *Metacortandracin*, and *Meticortin*. Prednisolone is available under the names *Metacorandralone*, *Deltasone*, *Hydeltra*, *Meticortelone*, and *Sterane*. Each steroid is available in 5-mg. tablets. It is difficult at present to state which of the 2 drugs is more effective. Boland (1956) after 6 to 9 months' trial in rheumatoid arthritis found prednisone and prednisolone of equal potency and effectiveness. They appeared to differ only in the variety of side effects each induced. Thus, it would appear that the drug of choice between the 2 steroids depends upon the minimal side effects induced by each in the patient.

**Methylprednisolone (Medrol).** Prednisone and prednisolone became available in 1955, and methylprednisolone followed in 1957. The structure of methylprednisolone is shown on page 830. This agent affords slight advantage over prednisolone in that its anti-inflammatory activity is slightly greater than that of prednisolone and its influence in causing sodium and water retention is somewhat less. The indications and precautions of methylprednisolone are the same as those of prednisolone; however, comparable results are usually achieved with ⅔ the dosage level. Methylprednisolone is available in 4-mg. tablets, the usual daily dose is 16 to 20 mg.

**Triamcinolone (Aristocort, Kenacort).** One year after the appearance of methylprednisolone, triamcinolone became available. Triamcinolone is 9α-fluoro-16α-hydroxyprednisolone as shown in the formula on page 830. Triamcinolone is more potent in its anti-inflammatory effects than methylprednisolone and causes less sodium and water retention. The indications and precautions in therapy are the same as those with prednisolone therapy. However, the achievement of comparable results requires lower dosage schedules. Triamcinolone is available in 1-, 2- and 4-mg. tablets. The range of maintenance dosage in rheumatoid arthritis is 2 to 15 mg. daily.

**Dexamethasone (Decadron, Deronil, Gammacorten).** Less than a year after the availability of triamcinolone, dexamethasone was made available (1958). Dexamethasone is 9α-fluoro-16α-methylprednisolone as shown in the formula on page 830. Dexamethasone is one of the most active anti-inflammatory steroids. As evidence of this statement, laboratory and clinical studies indicate that the anti-inflammatory activity of 0.75 mg. of dexamethasone is the equivalent of 4 mg. of triamcinolone, 5 mg. of prednisone, 20 mg. of hydrocortisone, and 25 mg. of cortisone. The greater potency does not of necessity confer upon dexamethasone decided therapeutic advantage over the other steroids previously discussed. Like the other potent steroids dexamethasone produces a minimum of sodium and water retention. However, the same indications and precautions discussed under the foregoing steroids prevail with dexamethasone therapy. Dexamethasone is available in 0.75-mg. tablets; in rheumatoid arthritis the daily dose is usually 1.5 to 3 mg. Dexamethasone is also available for the localized treatment of inflammation, such as 0.1 per cent ophthalmic solution containing neomycin sulfate.

The discussion of these synthetic steroids has indicated the great achievements that have been attained in organic chemistry in their synthesis and the therapeutic advantages that have accrued from their use.

**Paramethasone Acetate (Haldrone).** Among the newer fluorinated steroids is paramethasone acetate. Its formula is shown on page 830. Its potency is approximately ½ that of dexamethasone and 10-fold that of hydrocortisone when compared on a maintenance dosage basis in chronic diseases such as rheumatic arthritis. Clinical evidence indicates that the drug is qualitatively equivalent to dexamethasone, but quantitatively somewhat less potent. Suppressive doses in chronic diseases, in which steroid therapy is indicated, vary from about 4 to 8 mg. daily. Tablets are available containing 1 or 2 mg.

**Betamethasone (Celestone).** This compound is a newer fluorinated prednisolone derivative as shown chemically on page 830. It is claimed that betamethasone evokes a lesser degree of sodium and water retention. The potency of this steroid appears to be of the same order of magnitude as that of dexamethasone. This is indicated by the small dosage requirements. Thus, for suppression in chronic diseases, in which steroid therapy is indicated, the daily dose is from 1.2 to 3.6 mg. and maintenance daily doses range from 0.6 to 3 mg. Tablets are available containing 0.6 mg.

**Choice of a corticosteroid.** With the availability of numerous corticosteroids it is often difficult to decide upon a drug of choice. At the outset of this discussion it appears quite clear that prednisone and prednisolone offer therapeutic advantage over their predecessors cortisone and hydrocortisone in that there is a diminution of adverse side effects encountered. This is especially true with regard to sodium and water retention. The next question posed is, do methylprednisolone, triamcinolone, and dexamethasone offer definitive advantage over prednisone and prednisolone? As stated previously there has been achieved an increasing potency in their anti-inflammatory activity. Neustadt (1959) made a comparative study of these potent steroids in a group of 65 patients with active rheumatoid arthritis. His findings are most revealing. He stated, "No one preparation demonstrated any consistently superior therapeutic advantage. Factors influencing choice of treatment include probable effectiveness, nature of unwanted side effects, ease of administration, and cost to the patient." The effective maintenance dose was revealed in these studies; thus dexamethasone was most potent (1.4 mg.). Maintenance doses with methylprednisolone and triamcinolone were essentially the same, about 8 mg.; the maintenance dose with prednisone or prednisolone was 11.4 mg. The incidence of principal side effects observed by Neustadt are listed.

1. Moon facies, hirsutism, acne—same for all steroids studied
2. Gastrointestinal symptoms with and without ulceration—same for all steroids studied
3. Emotional disturbances, glycosuria and edema—significantly higher with prednisone and prednisolone
4. Ecchymosis and/or purpura—36 per cent with methylprednisolone, 23.6 per cent with triamcinolone, 14 per cent with prednisolone

Other side effects of a minor character are also mentioned by Neustadt.

It is clear that the limiting factor of corticoid steroid therapy in rheumatoid arthritis is the occurrence of adverse side effects. Therapy with any available steroid is not completely devoid of these; however, it is apparent that they can be minimized by the use of the potent steroids and by tailor-fitting the dosage schedule to the needs of the patient. Boland (1958) is of the opinion that the synthesis of the 16-methylated steroids represents a distinct advance.

We have passed through 15 years of clinical use of steroids in the treatment of rheumatoid arthritis, asthma, and other diseases. In retrospect it is clear that despite the striking advances that have been achieved, it is also necessary to recognize the risks involved in the long-term use of steroids. Often these risks preponderate over the expected advantages, and there appears to be a relatively small segment of clinical conditions in which the long-term use of steroidal therapy is justified.

**Fluorohydrocortisone Acetate.** The chloro-, bromo-, iodo-, and fluorocortisone and hydrocortisone derivatives have been synthesized. They are all 9 α-halogen substitution products, page 830. They exhibit adrenocortical activity. The fluoro derivative is most active, and fluorohydrocortisone is more active than fluorocortisone. Indeed, fluorohydrocortisone is more active in producing sodium retention in the adrenalectomized dog than desoxycorticosterone acetate. It is also effective in eliciting the deposit of glycogen in the liver of the adrenalectomized rat.

Fluorohydrocortisone acetate is effective in Addison's disease. It also exhibits strong antirheumatic action at a low dosage level of 1 to 2 mg. orally every 6 hours (Ward *et al.*, 1954). In rheumatic conditions the great disadvantage of fluorohydrocortisone acetate stems from its powerful action in causing sodium retention and edema.

When applied topically fluorohydrocortisone acetate appears to exhibit approximately 10 times the anti-inflammatory action of cortisone acetate. The product is used therefore most extensively in the form of an ointment or lotion. It is recommended and has been found effective in the same type of dermatoses as cortisone and hydrocortisone. The preparations available are *Florinef ointment* and *lotion* 0.1 and 0.2 per cent. *Alflorone Acetate* and *F-Cortef* are other brand names for these products.

The local ophthalmic use of corticosteroid therapy is not without its hazards. Extended use may increase intraocular pressure. In diseases causing a thinning of the cornea, perforation has occurred with the use of topical steroids. As a rule, the untoward systemic effects of the steroids are not encountered in their topical application.

**Physiologic considerations of cortisone and other corticosteroids.** At present it is clear that the principal value of cortisone and the other steroids discussed is obtained in the treatment of so-called "collagen diseases." Outstanding among these are rheumatoid arthritis and rheumatic fever. The diseases appear to possess a common denominator in a biochemical lesion responsible for the different syndromes. Many steroids appear to produce certain transient beneficial effects in the collagen diseases, especially rheumatoid arthritis. Their value is not constant nor do they produce the objective effect of the prompt reduction of the sedimentation rate. At the same time these steroids do not produce the untoward side actions elicited by cortisone and other active corticosteroids.

The physiologic and metabolic effects of the corticosteroids appear to be nonspecific. For instance, they occur when it is administered in sufficient quantity to normal as well as diseased individuals. However, the capacity of cortisone to mitigate the signs and symptoms of rheumatic, allergic, and collagen diseases appears to be specific.

Compared to its physiologic plasma level, massive quantities of the corticosteroids are required to afford relief. Hench *et al.* (1950) suggest that the corticosteroids may correct a relative, not an absolute, deficiency, and thus supply an increased tissue requirement for the hormone.

In effecting relief, the corticosteroids are not anti-infective in their action. They do not appear to remove or otherwise obliterate the unknown etiologic causative irritants in the diseases which they ameliorate. Indeed, they do not cure the diseases in which they are so effective in removing the symptoms. The corticosteroids appear to provide a barrier or buffer to protect the involved tissues against the causative irritants provoking the disease.

Hench (1952) uses an excellent figure of speech to account in a general way for the effect of cortisone and its derivatives: "This hormone appears not to extinguish the fire or to act like a carpenter to repair the damage of the fire. Instead, it appears to 'dampen the fire', or to provide, as it were, an asbestos suit behind which the patient, like some Biblical Shadrach, Meschach or Abednego, protects his tissues from the fire. If this protection is removed prematurely, before the fire has spent itself, the patient and his tissues will react again to the burning. But, if the protection is not discarded until the natural duration of the fire is over, the patient remains largely free of symptoms and apparently 'well'."

The anti-inflammatory activity of cortisone and other corticosteroids is not clearly understood. Some factors, however, appear to shed light on the process. It appears that in the inflammatory process a breakdown or disintegration of one cell promotes the destruction of other cells in the area. The products of cellular destruction are considered to act as phlogogenic stimuli evoking the classic picture of inflammation. Corticosteroids halt the inflammatory process by increasing the resistance of cells to the cytotoxic activity of the phlogogenic substances. Thus, at a molecular level the corticosteroids protect the cell by rendering it impermeable to the deleterious effects of the breakdown products of injured cells. In addition, the steroids produce improved capillary tone and selective permeability and thus diminish the exudation of plasma into the tissues.

Also it has been shown that hydrocortisone suppresses the capacity of the cell to elaborate phlogogenic stimuli. For example, Menkin (1954) showed that hydrocortisone suppressed the activity of *leukotaxine* and the formation of the leukocytosis-promoting factor (LPF). Hydrocortisone possibly owes its anti-inflammatory action to its capacity to suppress the cell's activity in producing the chemical agents responsible for inflammation. Furthermore, this action of hydrocortisone in an inflamed tissue where infection prevails provides an excellent opportunity for bacterial proliferation by suppressing the formation of the chemical factors involved in the inflammation process, principally LPF. Eyring and Dougherty (1955) state, "Any protective agent which will dilute, destroy, or lessen the destructive action of the broken cell or which will stabilize the action of the unbroken cell will lessen inflammation." They liken stress to systemic cellular alteration similar to local inflammation, which is diminished by hydrocortisone for the foregoing reasons.

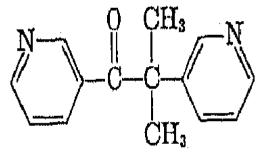
The mechanism of the production of peptic ulcer in steroid therapy is not clearly understood. Ulcer begins as an inflammatory condition of the mucosa, and the mucosal cells establish an inflammatory barrier against further irritation. The ulcerogenic property of the steroids likely stems from their capacity to break down the inflammatory barrier and render the incipient inflamed area vulnerable to further irritation.

The steroids, as such, are not chemical irritants to the mucosa. Besides, Robert and Nezamis (1962) showed that the ulcerogenic property did not stem from the release of histamine. They administered polymixin B to rats, which provokes histamine release from the tissues, until the stores of histamine were exhausted. In these animals the ulcerogenic capacity of prednisolone was unaltered.

It is clear that the dramatic clinical successes with ACTH and the corticosteroids have outrun our knowledge of their mechanism of action. Most observers agree that their action is in no way specific. The success of therapy likely depends upon the suppression of the inflammatory process by the corticosteroids and/or the protection of the tissue cells from injurious metabolites.

**Adrenal cortical inhibitors.** Fortunately, the incidence of diseases characterized by excessive adrenal cortical function, such as Cushing's syndrome and primary aldosteronism, are comparatively rare. It is clear however, that suppression of adrenal cortical activity, in these cases by means of drugs, would be beneficial. Certain drugs used for other purposes, such as thiouracil and streptomycin, have been shown to exert adrenal cortical suppression. The blocking of the renal electrolyte action of aldosterone spironolactone by Aldactone A is discussed on page 804. Other compounds are being investigated that have shown marked adrenal cortical suppression. Among these are the insecticide DDD (tetrachlorodiphenylethane) and amphenone B and its derivatives. The derivatives of amphenone B appear to offer therapeutic possibilities.

Amphenone B is 3,3-bis[*p*-aminophenyl]-butane. A compound related to amphenone B containing 2 pyridine groups in place of the 2 aniline groups of the parent compound was synthesized and studied by Chart and Sheppard (1959). This compound, first designated as Su-4885 and now as Metopirone and Methopyrapone appears to be more specific and fraught with fewer side effects than amphenone B. Metopirone appears to block 11 $\beta$-hydroxylation of steroidal molecules in the adrenal cortex. When Metopirone is administered to dogs or man, it inhibits the secretion of all 17-ketosteroids, which in turn causes an outpouring of ACTH. The plethora of ACTH fails to correct the suppression of hydroxycortisone production. This differentiation of excretion of the adrenal corticoids serves in the differential diagnosis of pituitary-adrenal dysfunctions. The structure of Metopirone is shown in the formula:



Metopirone, Methopyrapone
2-Methyl-1,2-di-3-pyridyl-1-propanone

The available preparation of this agent is Methopyrapone Ditartrate. It is administered intravenously 30 mg./kg. in 1 l. of saline solution every 4 hours for six doses.

*In vitro* studies suggest that the suppression of the adrenal cortex by Metopirone is associated with diminished glucose utilization by the adrenal glands. Of further interest is the fact that Metopirone stimulates the release of catecholamines from the adrenal medulla.

The discovery of the specificity for the adrenal cortex of Metopirone is a definitive advance in our knowledge in this fertile field of pharmacologic investigation.

### Treatment of the Arthritides

One of the most distressing and disabling syndromes which is encountered in medical practice is that of *arthritis*. The metabolic disturbances responsible for joint pain and dysfunction are at long last being partially understood. With the development of *adrenal corticotropic hormone* and *adrenocortical steroid therapy*, these obscure metabolic changes are slowly being elucidated. Besides, therapy in the arthritides has been improved. We shall give consideration to the drugs used in the treatment of the arthritides.

**Historical introduction.** Rheumatism is one of the oldest diseases known to man. It is probably many thousands of years older than man. It likely goes back to the first bony joint that began to show signs of old age and the strain of survival. Recent discoveries show that it existed in ancient Egypt. Excavated mummies have been found which exhibit the hypertrophic joints that characterize degenerative arthritis. This painful condition of the ancient Greeks was noted by Hippocrates. Galen furnished case reports of the old Romans who suffered from rheumatism.

In its modern sense the word *rheumatism* did not appear until 1642, when the works of Guillaume de Baillou posthumously appeared. Sydenham described acute rheumatism in 1666. Heberden in "De Arthritide" in 1788 described the nodules in the fingers which occur in osteoarthritis. He called them "Digitorum nodii" but today they are known as *Heberden's nodes*. The term *rheumatoid arthritis* was first proposed by A. B. Garrod in his book on gout in 1857.

Rheumatism has been called the "Great Crippler" and the "King of Human Miseries." The terms are not exaggerations. In the acute stages, the pain is unremitting and the misery of its victims is pathetic. One out of ten cases of rheumatoid arthritis progresses to the crippling stage. Once the disease has developed, 58 per cent of the patients are unable to carry on their work.

Although rheumatism is one of the oldest known diseases and affects a large percentage of the population of the world, paradoxically it is probably one of the diseases most neglected by medicine. Statistical studies indicate that 10 million people in the United States suffer with some form of rheumatism. True arthritis has an incidence of 4.5 million, 200 thousand are disabled and 800 thousand are partially disabled. The estimated wage loss owing to the disease is 700 million dollars annually.

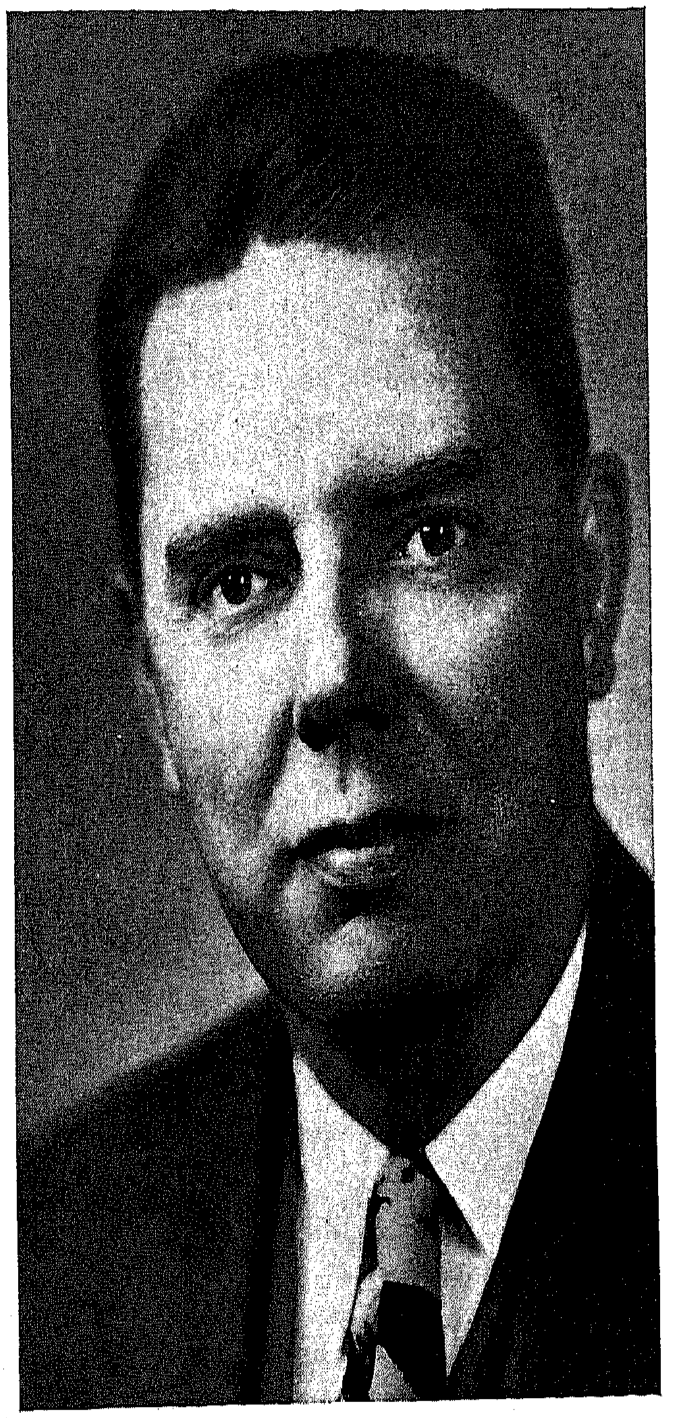
The beginning of the development of satisfactory therapy for this disease may be the recent investigations in Sweden by Carlstroom and Lovgren on adenosine triphosphate; in England by the Scientific Advisory Committee of the Empire Rheumatism Council on the etiology and clinical features of rheumatoid arthritis; and in this country by Hench, Kendall, Thorn, and others, with the development of cortisone and ACTH. Only time will give the answer, but a new physiologic approach to the rheumatic state has been given momentum, and a great deal of interest and attention has been refocused on the oldest and most neglected disease of man.

**Classification of the arthritides.** Rheumatism is a lay term that embraces a large number of medically-described conditions. For a classification of the variants of rheumatic disease see Table 53-1.

**Rheumatic fever.** Acute rheumatic fever is an acute phase of a chronic disease associated with group A beta hemolytic streptococcal infection. It is characterized by *fever, joint swelling* and *immobility, polyarthralgia endocarditis, pericarditis, toxemia*, and a *high sedimentation rate*. It has a high incidence among school children, especially at the lower socio-economic levels. The disease is believed to account for 98 per cent of all cardiac disorders in patients under the age of 20 years.

*Treatment with salicylates.* The treatment is outlined as follows:

1. The patient is put to bed with adequate nursing care.
2. Sodium salicylate or aspirin (the two drugs are equally effective) is given in doses from 5 to 10 gm. a day in 6 doses 4 hours apart. Sodium bicarbonate is given with each dose in quantities equal to half of the salicylate administered. The plasma level of salicylate is lowered by the use of sodium bicarbonate, and the urinary excretion is enhanced. Gastric irritation is also diminished by the use of sodium bicarbonate. The drug is best tolerated after meals. Milk and crackers given simultaneously diminish the gastric distress.
3. There will generally be some symptoms of salicylism such as tinnitus, anorexia, and nausea. If *nausea, vomiting, deafness*, and *tachypnea* persist, the patient's tolerance has been exceeded, and the dosage schedule should be reduced.
4. The temperature falls within 24 to 48 hours. Joint pains and swelling subside. The salicylate is continued for 2 weeks. The decline of the elevated sedimentation rate begins after the first week.
5. Although salicylates produce a dramatic improvement in the patient's condition in the acute attack of rheumatic fever, there is no proof that the salicylates shorten the course of the disease.
6. After the subsidence of the acute attack of rheumatic fever, penicillin or sulfadiazine is administered for long periods and perhaps indefinitely to prevent the recurrence of the acute phase of the disease.



PHILIP S. HENCH

*Eminent American clinician who first used cortisone in arthritis*

"Usually, the fibrositic component (muscular and articular stiffness) began to diminish first, often within the first 48 hours . . . and often was markedly or completely relieved within a few days."

The mechanism of the action of the salicylates in rheumatic fever is not understood. Their value in the relief of the symptoms in the acute attack of the disease appears to be due to the following action of salicylates.

1. Salicylates reduce body temperature mainly through increased heat loss.
2. They exert an analgesic action and hence diminish pain.
3. Although much has been said about the value of salicylates in increasing uric acid excretion and increasing the permeability of the blood vessels so that metabolites pass from the tissues to the blood, the evidence is not convincing that this plays an important role in the treatment of rheumatic fever.
4. Undoubtedly one of the greatest factors of the action of the salicylates is the relief that they afford the patient from the emotional trauma of fever, pain, and insomnia.
5. In addition to the foregoing effects of salicylates which are beneficial in rheumatic fever, another factor appears to be signifi-

TABLE 53-1

*(Smyth 1960)*

*Connective Tissue Disorders Accepted as Rheumatic*

I. Articular

A. Inflammatory

(1) Idiopathic
  i. Rheumatic fever
  ii. Rheumatoid arthritis
  iii. Atypical forms of RA
    (a) Psoriatic
    (b) Juvenile
    (c) Felty's syndrome
    (d) Sjögren's syndrome
  iv. Special forms of arthritis
    (a) Ankylosing spondylitis
    (b) Intermittent hydrarthrosis
    (c) Palindromic rheumatism
(2) Infectional (due to specific infection)

B. Degenerative

(1) Degenerative joint disease
(2) Osteochondrosis
(3) Intervertebral disc syndromes

II. Non-Articular

(1) Bursitis
(2) Fasciitis
(3) Fibrositis
(4) Myositis
(5) Neuritis
(6) Periarthritis
(7) Tendinitis
(8) Tenosynovitis
(9) Panniculitis

cant. The beneficial effect of ACTH in arthritis and rheumatic fever is definitely established. Sayers *et al.* (1946) showed that adrenal cortex-ascorbic acid depletion is a reliable measure of the adrenal cortex activity. The possibility of eliciting the secretion of ACTH from the pituitary, and the subsequent production of increased cortical activity, suggested itself as a possible mechanism of salicylate activity in rheumatic fever. Cronheim and King (1952) found that salicylates produce a significant depletion of adrenal-ascorbic acid in rats. The depletion appeared to be proportional to the blood-salicylate level. The activity was not manifested in hypophysectomized animals. Several substituted salicylic acids and 12 aliphatic acids were found to be ineffective. However, benzoic acid produced ascorbic acid depletion, but its action was not so marked as that of salicylic acid.

There are many objections to the hypothesis that the mode of action of the salicylates in rheumatic fever is through the pituitary-adrenal system. It was shown by Smith (1952) that meta and para hydroxybenzoic acids each elicit a significant reduction in adrenal ascorbic acid when injected into rats with unaltered pituitary glands. Neither of these isomers of salicylic acid is active against rheumatic fever.

Further, Feeney *et al.* (1955) observed that acetophenetidin caused adrenal ascorbic acid depletion. Its chemical configuration is dissimilar to that of salicylic acid. Another factor which seems to invalidate this hypothesis is the antagonism of effects on tissue metabolism between salicylates and cortisone. For example, cortisone increases liver glycogen deposition in adrenalectomized rats; salicylates decrease liver glycogen. The same antithesis of response holds for the glycosuria of diabetic rats. And further, the glycosuria elicited in rats on a high carbohydrate diet with cortisone is diminished by salicylates. Again, it has been observed that aspirin was capable of suppressing the glycosuria in partially depancreatized rats prior to and after adrenalectomy, indicating that the action is not mediated through the adrenal glands.

Herndon *et al.* (1958) studied the acute effect of aspirin (30 mg./kg. every 2 hours in 3 doses) on patients with rheumatoid arthritis and healthy subjects, with regard to plasma concentrations of corticoids and urinary steroid excretion. They observed that: (1) the diurnal response to ACTH of free plasma reducing steroids was the same in each group; (2) aspirin evoked an acute decrease of about 40 per cent in the total plasma level of corticoids. Some degree of reduction persisted for 48 hours in the healthy subjects; (3) plasma corticoid response to ACTH was reduced in both groups by the administration of aspirin; (4) aspirin increased the urinary excretion of neutral 17-ketosteroids and both free and conjugated corticosteroids. These investigators are of the opinion that the effect of aspirin in evoking a fall in the plasma corticoid level is secondary to the action of the drug in promoting increased urinary excretion.

Although it may be argued that the more or less rapid return to normal of the plasma corticoid level would require pituitary stimulation, this appears to be a sequential effect of a low hydrocortisone-plasma level rather than a direct action of aspirin on the pituitary. The animal data and these studies in man suggest that the mechanism of action of salicylates in rheumatic fever through the pituitary-adrenal axis remains to be established. Furthermore, from the evidence available, the depletion of ascorbic acid from the adrenals in rats elicited by a massive dosage of salicylates appears to be a nonspecific action and a stress response of the animals' pituitary-adrenal system. Of further interest is the work of Stephenson (1960) who showed that salicylates administered to immature rats induced atrophy of the thymus gland. This action was direct and not mediated through the pituitary adrenal system. He states, "No evidence was found to indicate that salicylates potentiate the thymolytic action of adrenal corticosteroids."

The consensus agrees that the beneficial effect of the salicylates in the acute phase of rheumatic fever is not mediated through the release of ACTH and the sequential secretion of corticosteroids. Nevertheless, either ACTH or prednisone appears to be equally as effective as salicylates. The untoward effects of the corticosteroids in rheumatic fever are not encountered so frequently as they are in long-term therapy such as is required in rheumatoid arthritis or asthma. However, they do occur and may be serious. The question of which of the 2 types of therapy provides the more effective myocardial protection is still polemic. It is often befogged in comparative studies by time differences in the onset of treatment. There appears to be general agreement that steroidal therapy is always indicated in severe cases which have not been brought under control by salicylates.

**Sodium $\gamma$-resorcylate in rheumatic fever.** The specificity of salicylates in rheumatic fever is difficult to understand, especially since meta and para hydroxybenzoic acids do not exhibit this property. It is well known that the molecule of salicylic acid is capable of *chelation*, page 948, whereas neither the meta nor para isomers possesses this property. Reid *et al.* (1951) assumed that this property of salicylate played a role in its effectiveness in rheumatic fever. Accordingly, they prepared $\gamma$-resorcylic acid, which possesses the property of dual chelation. This compound was found effective in rheumatic fever at a dosage level of 800 mg. daily. Like the salicylates, sodium $\gamma$-resorcylate depletes the ascorbic acid content of the adrenal cortex when injected into rats. That chelation is a prime factor in the therapeutic action of the salicylates, however, remains to be proved. It is of interest that Clarke *et al.* (1956) employed another polyhydroxybenzoic acid in the treatment of rheumatic fever with promising results. The compound used was phloroglucinol carboxylic acid which is 2,4,6-trihydroxybenzoic acid. The compound was administered in doses of 1 to 1.3 gm. daily in divided doses. There appeared to be no untoward effects in their limited series of cases. The acute manifestations of the disease were suppressed in 2 to 3 days. These investigators hold the view that the antirheumatic activity of phloroglucinol carboxylic acid is 8 to 10 times greater than either salicylic or gentisic acids.

Related to these studies is the interesting work of Crabtree *et al.* (1958). They studied the oxidative metabolites of salicylates in normal and fevered rats using $C^{14}$-labeled compounds. Of special interest is the fact that gentisic acid was found in the region of the pituitary in fevered animals but not in normal animals. The metabolites of salicylate reported were carboxyl $C^{14}$, gentisic acid, 2-acetyl gentisic acid, and 2,3,5-trihydroxybenzoic acid.

**Rheumatoid arthritis.** One of the most prevalent forms of rheumatic disorders is rheumatoid arthritis. It is a systemic disease, and general symptoms ultimately occur. The criteria for diagnosis are definite: symmetric involvement of the smaller joints with resultant muscular weakness and atrophy, subcutaneous nodules, and elevated sedimentation rate. Agglutination tests with *hemolytic streptococci* are usually positive. X-ray changes of osteoporosis and narrowed joint spaces usually appear within 9 to 12 months. Women are affected 3 times as frequently as men. The prevalence of the disease is demonstrated in a recent epidemiologic survey in Pittsburgh, which showed an incidence of 2.7 per cent in persons over 14 years of age.

*General measures.* Of first consideration should be rest, physiotherapy, and relief from pain. The rheumatic patient should have 12 to 14 hours of rest, both physical and mental, a 10-hour period at night and a 1- to 2-hour period in mid-afternoon. The physiotherapy treatment is of great importance. The regular daily use of heat and massage is essential. Short wave diathermy, administered by a physiotherapist, is employed effectively in acute stages.

**Specific aims of drug therapy.** The specific aims of drug therapy in arthritis are to *relieve pain, reduce the joint swelling, increase joint mobility, check the narrowing of the joint space,* and *reduce fever* if present. Most authorities appear to agree that this should be achieved by conservative drug therapy if possible. Recourse to more drastic forms of drug treatment are reserved for refractory cases.

**Salicylates in arthritis.** To accomplish the previously mentioned aims of therapy, salicylate in the form of aspirin, is the first drug of choice. A discussion of its use and mechanism of action is found on page 840. As much as 5 to 10 gm. daily can be administered depending upon the patient's tolerance.

Despite the dramatic rapid remissions which are achieved in rheumatoid arthritis with the corticosteroids, the preferred therapy in most cases is aspirin. The treatment is fraught with fewer side effects, and although the immediate results are not usually so dramatic, evidence which is substantial has been accumulated to show that over extended time periods aspirin therapy does not suffer by comparison.

At the onset of the disease, to obtain rest and pronounced analgesia it is advisable to prescribe codeine phosphate (30 mg.) 3 to 4 times a day, or dextropropoxyphene (Darvon), 65 mg., to be taken with the salicylate dose when pain is severe and on retiring. Patients with arthralgic pain have used codeine as an analgesic for years without showing tolerance or addiction. Mild sedation with phenobarbital, 15 to 30 mg., is recommended. Meprobamate is useful because it contributes skeletal muscle relaxation with its tranquilizing action.

**Corticosteroids in arthritis.** If success is not achieved with salicylate therapy, recourse to the corticosteroids is considered. As previously mentioned, the anticipated therapeutic benefits must be weighed against the risks involved. This is a long-term investment in drug therapy. Here best results are achieved by tailor-fitting the steroid to the patient's needs and keeping the dosage level low to reduce side effects to a minimum. Expense to the patient may also be an important factor. Prednisone and prednisolone are official steroids that are reasonably inexpensive and usually effective without too serious side effects. Of the more potent and more expensive agents in this class, Boland (1961) prefers triamcinolone or dexamethasone as drugs of choice in rheumatoid arthritis.

**Antimalarial drugs in arthritis.** Certain antimalarial drugs such as quinacrine and chloroquine have been observed to exert a benign anti-inflammatory action in patients with *lupus erythematosus*. Chloroquine appeared to be more useful than quinacrine, as it was better tolerated in long-term therapy and did not produce pigmentation of the skin. The success of chloroquine therapy in the inflammatory condition of lupus prompted its use in the treatment of rheumatoid arthritis (Haydu, 1953). Many clinical studies of the use of chloroquine and Plaquenil (hydroxychloroquine) in arthritis have indicated that these antimalarial drugs are beneficial in a segment of arthritic patients. Besides, their use does not preclude adjunctive therapy.

There appears to be no rational basis for the comparative success of the antimalarial drugs in the treatment of rheumatoid arthritis. The concept proposed by Haydu (1953) that their action is dependent upon their capacity to inhibit ATPase appears untenable. The view of Rinehart (1955) that the drugs may exert an antimetabolic action does not offer any adequate basis for their use. From the evidence available their use is empiric.

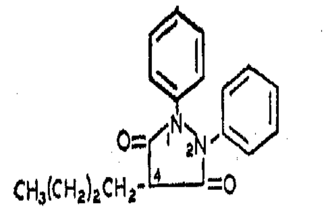
The drug of choice appears to be Plaquenil; its toxicity in laboratory animals is approximately ⅕ that of chloroquine. However, some clinicians prefer chloroquine. For example, Cohen and Calkins (1957) using chloroquine phosphate in a double blind study reported 80 per cent improvement in their patients using the criteria of the American Rheumatism Association. They used a daily dose of 500 mg. Side effects encountered were *blurred vision*, *epigastric burning sensation*, and *nausea*. Two patients developed *leukopenia* which was transitory.

Scherbel *et al.* (1958) studied chloroquine or Plaquenil in a series of 800 patients with rheumatoid arthritis and its variants for a period of 3 years. Of special significance is the observation that improvement occurred slowly in 52 per cent of 106 patients with rheumatoid arthritis. Thus, only 25 per cent showed marked improvement after 3 months' treatment, but after 12 months' treatment this percentage had risen to 37 per cent. Steroid therapy along with the antimalarial drugs reduced the period of latency before significant improvement occurred. Approximately ½ of the patients receiving therapy exhibited some type of untoward reaction to the drugs. The period of latency before expected improvement was considered by these investigators to be a definite disadvantage of this form of therapy in arthritis.

The initial dose of Plaquenil is 400 to 600 mg. (1 tablet, 2 or 3 times daily), the maximal dosage is 1000 mg. daily. Maintenance dosage is 200 to 400 mg. daily. As suggested previously steroidal therapy may be instituted simultaneously. Likewise, salicylate therapy is compatible with Plaquenil medication.

It is difficult to evaluate the place of the antimalarial drugs in rheumatoid arthritis. From the numerous reports in the literature it appears to the authors that they are useful in a segment of the arthritic population, but at present they should be considered after failure of intensive salicylate therapy.

**Phenylbutazone (Butazolidin) in rheumatic disease.** Butazolidin is a pyrazolidine derivative that is useful in the treatment of arthritis and certain allied conditions. Chemically, the substance is 3,5-dioxo-1,2-diphenyl-4-*n*-butylpyrazolidine, as shown in the accompanying formula.



Butazolidin
(Phenylbutazone)

The compound is a white or slightly yellow crystalline powder. It is insoluble in water.

Butazolidin was developed in Switzerland. It exhibited a solubilizing effect on aminopyrine, and the mixture of equal parts of the 2 compounds was used extensively in Europe under the name of *Irgapyrin*. In America, Butazolidin alone has been given a most extensive clinical trial in various arthralgic states.

**Pharmacologic properties of phenylbutazone.** Wilhelmi (1949) demonstrated that Butazolidin had a marked capacity to raise the threshold to pain in laboratory animals. It also evoked antipyretic properties in hyperpyrexic animals. The compound exhibited anti-inflammatory properties in animals similar to cortisone. Large doses produced tonic-clonic convulsions. In rats, daily doses of 50 mg./kg. elicited no apparent chronic toxicity.

Kuzell *et al.* (1953) demonstrated in rats that the action of Butazolidin was not mediated through the pituitary-adrenal cortex axis. There was no decrease in adrenal ascorbic acid or decrease in total eosinophil counts following the administration of Butazolidin to either intact or hypophysectomized rats. Experimental polyarthritis in rats was aggravated by the giving of Butazolidin. This effect is similar to that experienced with ACTH and cortisone.

Tissue respiration studies showed that Butazolidin inhibits the oxygen consumption of brain and the utilization of glucose by tissue.

Butazolidin causes sodium retention, and its use may lead to edema. Burns *et al.* (1953) showed that Butazolidin did not increase the excretion of potassium. The excretion of uric acid is increased.

Burns *et al.* (1953) demonstrated that Butazolidin is slowly but completely metabolized in man. The rate of biotransformation varies with different subjects from 10 to 40 per cent a day. The products of metabolism are a derivative of Butazolidin with a hydroxyl group in the para position of one of the phenyl groups and another with a hydroxyl group in position "3" of the butyl side chain (Burns *et al.*, 1955). These investigators determined that sodium retention begins at plasma levels of 5 mg. per cent. About 10 mg. per cent is required for the anti-inflammatory properties in rheumatoid arthritis.

**Butazolidin in arthritis.** Butazolidin has had extensive clinical trial in the arthritides. Most reports coming to our attention bespeak the fact that the drug is frequently effective in relieving pain, stiffness, and swelling, and increasing mobility. Its use, however, must be enjoined with great care and meticulous vigilance of the patient's blood picture.

Butazolidin is given in arthritis in doses of 300 to 600 mg. daily in divided doses. Tablets are red coated and contain 100 mg.

If therapeutic results are not achieved within a week, it is doubtful if improvement will result with this form of therapy. As soon as the patient's symptoms and signs are improved, the dose should be reduced to minimize the possibility of serious side effects. Certain individuals may be maintained on a dosage of 100 mg. daily (Smith and Kunz, 1952). These investigators evaluated Butazolidin in 140 cases of rheumatoid disorders. These included 48 cases of rheumatoid arthritis and gout. Some improvement was experienced in all of these cases. In other types of arthritis beneficial clinical effects were observed also.

Butazolidin is an irritant to the gastrointestinal mucosa. It may activate dormant ulcers. Therefore, it is advisable to give the tablets with milk. Raffensberger (1953) observed multiple gastric ulcers occurring in a patient during Butazolidin therapy. Krainin (1953) had a patient on Butazolidin therapy who developed a gastric ulcer with massive hemorrhage. The drug appears to be interdicted in the patient with a history of ulcer or chronic dyspepsia. Owing to sodium retention caused by Butazolidin, one must be cautioned against its use in patients with congestive heart failure and hypertension. It should never be administered casually as a simple analgesic. The most serious side effects of Butazolidin are those upon the hematopoietic system. This action is shared by its companion drug aminopyrine, page 462. Steinberg *et al.* (1953) reported a fatal case of agranulocytosis following Butazolidin therapy. Others have also observed blood dyscrasias. *Its use must be employed with a careful follow-up of the patient's blood picture.*

Kuzell *et al.* (1953) attempted to establish a relationship between the therapeutic value of Butazolidin in various rheumatic disorders and its concomitant side effects. To illustrate, in gout good therapeutic results were achieved in 83 per cent of the cases, and 7 per cent experienced serious toxic side effects. Thus, the clinical ratio in gout is 11.9. Other ratios were far less favorable; psoriasis with arthritis, 6.1, rheumatoid spondylitis, 4.7, rheumatoid arthritis, 3.8, and painful shoulder, 3.4. In other conditions the ratios were even less favorable. The evidence seems clear that the drug brings about remissions in many rheumatic disorders followed by a relapse when the drug is withdrawn.

Mauer (1955), in a review of the literature, reported a total of 24 deaths from the use of Butazolidin. In from 10 to 15 per cent of the cases in which it is used the therapy was discontinued owing to toxic side effects.

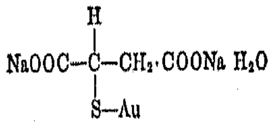
Platt and Steinberg (1957) studied the action of prednisone alone and in combination with Butazolidin and with salicylates in the treatment of rheumatoid arthritis. Nine of ten patients preferred Butazolidin and prednisone to prednisone and aspirin. Unfortunately, only 4 patients tolerated prednisone and Butazolidin therapy for prolonged treatment. Gastrointestinal irritation and ulceration appeared to be the principal adverse side effect. Incidence of peptic ulcer was more frequent with combined Butazolidin and prednisone therapy than with prednisone alone.

One of the most difficult problems in therapeutics is to evaluate critically a drug used in the treatment of rheumatoid arthritis. Many attempts have been made with Butazolidin, and in a segment of the patients, it appears to be a valuable drug. Nevertheless, from the toxic manifestations which might occur with Butazolidin therapy, it is clear that it should not be used as an alternative analgesic in arthritis. There appears to be no evidence of its eliciting a curative action; it should therefore be used only in patients in whom less potentially toxic agents have failed to afford relief.

**Gold therapy in arthritis.** Gold compounds have been used in the treatment of such conditions as tuberculosis, lupus erythematosus, asthma, and arthritis. The use of gold compounds in *rheumatoid spondylitis*, *degenerative arthritis*, and *fibrositis* has been most disappointing. However, in *rheumatoid arthritis*, gold therapy may achieve success. Hench (1947) reported that about half of the cases of rheumatoid arthritis treated with gold therapy obtain symptomatic relief. Improvement with gold therapy usually does not become manifest until after 1 to 3 months of treatment. This makes the assessment of the value of the treatment difficult since rheumatoid arthritis is characterized by spontaneous remissions.

There are 3 gold compounds generally employed. These are *gold and sodium thiosulfate*, *aurothioglucose* (*Solganal*) and *gold sodium thiomalate;* each is recognized in the National Formulary. The most generally used gold salt appears to be gold sodium thiomalate (Myochrysine).

Gold sodium thiomalate is a soluble gold salt containing 50 per cent of gold. Its structure is shown in the accompanying formula.



$$\mathrm{NaOOC{-}\overset{\displaystyle H}{\underset{\displaystyle S{-}Au}{C}}{-}CH_2{\cdot}COONa\ H_2O}$$

Gold Sodium Thiomalate, N.F.
(Myochrysine)

In the treatment of active rheumatoid arthritis, initial doses of 10 to 15 mg. of Myochrysine are administered intramuscularly to test the sensitivity of the patient to gold. If no untoward effects develop, the usual treatment is instituted. This consists of 25 to 50 mg. of the gold salt intramuscularly at weekly intervals. A total dosage of 700 to 2000 mg. of the salt may be given in a single course of treatment. It is believed to be safer to keep the total dosage at 500 to 1000 mg. A minimum of 2 courses is generally given with a 6- to 12-week interval.

Gold salts are not generally beneficial in arrested cases of rheumatoid arthritis. The most favorable results are achieved in the early stages of rheumatoid arthritis. Adams and Cecil (1950) found gold useful in Still's disease or juvenile rheumatoid arthritis, but of little value in spondylitis. Since the use of steroid therapy in rheumatoid arthritis, gold salts are usually not indicated except for refractory cases.

**Toxicity and fate of gold.** Gold is a potentially toxic metal. Its soluble salts produce a toxicologic syndrome in animals similar to that caused by arsenic compounds, page 164. Clinically, the use of gold salts is fraught with serious hazards. *Erythema*, *pruritus*, *urticaria*, and *skin rash* often occur with the injection of gold salts. Very serious reactions to gold are less frequent but are very dangerous when they do occur and may be fatal. These reactions include *renal irritation*, *exfoliative dermatitis*, *ulcerative enteritis*, *leukopenia*, *thrombocytopenia*, *agranulocytosis*, and *aplastic anemia*. The seriousness of these reactions bespeaks the necessity for extreme caution in the administration of gold salts.

The intramuscular injection of gold salts gives rise to plasma concentrations of gold which are only very slowly diminished. High concentrations are retained by the kidney for months after a single injection. Gold is excreted mainly by the kidney in the urine. Approximately 20 per cent is excreted in the feces.

**Dimercaptopropanol (BAL),** page 950, has been shown to be useful in the amelioration of the various toxic manifestations of gold salts. BAL appears to increase the urinary excretion of gold.

Skin reactions to gold therapy have responded favorably to the administration of *vitamin* $B_{12}$. Lesions have been reported to subside rapidly, and pruritus without lesions is frequently terminated. The vitamin is given in a dose of 15 $\mu$g. with each injection of the gold salt. The antihistaminic drugs have been found useful in preventing a "flare up" of the arthritic process which occurs in a small segment of patients 24 to 48 hours after the administration of gold salts.

**Mechanism of action of gold salts.** The mode of action of gold salts in rheumatoid arthritis is obscure. It has been stated that patients with rheumatoid arthritis usually show positive agglutination tests with *hemolytic streptococci.* Gold salts are bactericidal and show a high degree of activity against the hemolytic streptococci. It is, however, doubtful that this fact alone is responsible for the beneficial results of gold in rheumatoid arthritis. However, Dawson and Hobby (1940) found that Myochrysine would protect mice against 1000 lethal doses of streptococci hemolyticus. Gold salts are readily reduced to metallic gold. It is possible that the gold particles in the circulation elicit a response from the reticuloendothelial system which is beneficial in infectious arthritis. The hypothesis has been proposed that gold-salt therapy in rheumatoid arthritis is perhaps a form of stress therapy involving the adrenal cortex. However, no increase in the urinary excretion of 17-ketosteroids has been observed in patients treated with gold salts for arthritis and showing improvement in their condition.

Implicit in these statements is the fact that there is no rational explanation of the beneficial effects of gold salts in a number of rheumatoid arthritic persons. This, however, should not be disturbing because the same statement holds for the antimalarial drugs and to a lesser degree with other of the agents used in the control of the disease. Robinson *et al.* (1956) commented as follows: "After 30 years of the use of gold salts in arthritis the precise value of this therapy remains uncertain. It can be concluded, however, that the gold-induced remission of arthritis cannot be extended indefinitely and that gold therapy does not alter the ultimate course of the disease."

But gold salts continue to be used in this baffling disease. For example, Jeffrey (1962) used 2 matched groups in 100 each of rheumatoid arthritic patients in a double blind study. Each group received salicylates and physical therapy as required. The controls received 0.5 $\mu$g. of Myochrysine and the treated group 50 mg. of the salt weekly for 20 weeks. At the end of 6 months the treated group showed double the number of patients in top functional grade with quiescent joints as did the control group. The high incidence of dermatitis (21) in the treated group was disturbing. Studies of this kind convince the authors that gold salts in arthritis will be with us for some time to come.

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# 54

# *Carbohydrate Metabolism and Insulin*

"The oxidation of glucose by the human body is one of the most fundamental and important phenomena of nature."

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**Historical development of carbohydrate metabolism.** Our modern knowledge of the fate of sugar in the animal body is a little more than a century old. The initial step was the discovery of glycogen by Claude Bernard in 1857. He called the polymerized glucose molecules glycogen (meaning sugar former) and also referred to it as *animal starch.* About a decade later Langerhans discovered the islet tissue in the tail of the pancreas. He believed these aggregations to be lymphoid cells, but this view was not tenable since they failed to hypertrophy in leukemia.

Twenty years later von Mering and Minkowski performed their classic experiments on dogs. By pancreatectomy they were able to produce the cardinal symptoms of diabetes in the animals. Prior to this time the liver, kidneys, and bladder had been incriminated as the locus of the disease *diabetes mellitus.* The etiologic site of the disease was established as the pancreas.

For a third of a century biochemists and pharmacologists made efforts to extract the active *antidiabetic principle* from the islet tissue of the pancreas. For the most part these efforts were uniformly unsuccessful until the work of Banting and Best in 1921. The dramatic story of the discovery of insulin is given in Banting's own words on subsequent pages. With insulin, not only was the successful treatment of diabetes made possible, but with it, investigators now had a useful tool to elucidate the various ramifications of carbohydrate metabolism. In addition to the role of insulin in carbohydrate metabolism it has now been shown to affect growth and protein, and fatty acid metabolism.

The role of the anterior lobe of the pituitary body in diabetes mellitus was demonstrated by Houssay and Biasotti (1931 *et seq.*). They showed that the symptoms of diabetes produced by the ablation of the pancreas in dogs could be greatly mitigated by hypophysectomy. It became evident that the pituitary gland elaborates a principle capable of acting as an antagonist to the action of insulin.

In 1943 Goldner and Gomori confirmed the work of Dunn *et al.* (1943) who showed that alloxan (mesoxalylurea) produced diabetes in rats by a specific action on the *beta cells* in the islet tissue. This has been demonstrated in other animals, and subsequent investigation has shed further light upon the nature of the varied metabolic patterns of this and other forms of experimental diabetes in different species.

The discovery of the hypoglycemic effect of the sulfonylurea compounds and their use as oral antidiabetic drugs by Franke and Fuchs (1955) brought about a resurgence of interest in diabetes and control of carbohydrate metabolism.

**Diabetes mellitus.** The principal use of insulin is in the treatment of diabetes mellitus. It provides replacement therapy. The disease was recorded in the Papyrus Ebers. It was referred to as *honey urine* and a *melting away of the flesh* in the urine. In 1776 Matthew Dobson discovered a chemical method of proof that the sweetness of diabetic urine was due to the presence of glucose.

Some progress was made in the dietary management of the disease during the 19th century. But in the first 2 decades of the present century the dietary control of diabetes was greatly advanced by the distinguished American clinicians E. P. Joslin, F. M. Allen, and others. Carbohydrate was limited in the diet. Most of the calories of the diet consisted of protein and fat. Acidosis and coma were frequently encountered, and in the young person diabetes was usually a rapidly fatal disease.

The disease is characterized by clinical symptoms resulting from real or apparent insufficient pancreatic secretion of insulin or possibly overabundance of some insulin-inhibiting factor such as hypersecretion of the anterior pituitary or adrenal gland. The result is an elevated blood sugar level and concomitant *glycosuria* tending toward *ketosis.* The loss of carbohydrate results in *polyphagia* and *asthenia; water balance is disturbed* and *polyuria* and *polydypsia* follow.

The failure of normal utilization of glucose in the tissues is accompanied by increased production of fatty acids which are formed more rapidly that they can be consumed. Fragments such as *acetone* and *beta hydroxybutyric acid* are formed in excessive amounts and accumulate in the blood and tissues. The presence of these compounds produces acidosis, ketosis, finally coma, and death. Joslin spoke of coma as the "Sword of Damocles" over the head of the diabetic.

The discovery of insulin changed the entire pattern of the treatment of diabetes. It provided hope where previously there had been only despair. In the early insulin days Joslin in his inimitable style wrote:

> "The scenes are shifted and the actors changed. No longer is the setting Youth and the villain Coma, but the stage is arranged for an Old Age act and an old actor named Arteriosclerosis, renowned for the multiplicity of his roles. Coma was cunning and clever and oft secured his shining mark, but Knowledge and Education now thwart him where formerly Chance failed. Arteriosclerosis is almost always successful if he is given time, but he, too, is sometimes restrained by Knowledge and Education and has been persuaded now and then to consent that Old Age shall end the play. For what he was rather than for what he is, the first place in a discussion of causes of death in diabetes is still given to Coma, chiefly to point out that this villain should no longer be permitted to take any part, because Knowledge and Education have been joined by Insulin."

The increased life expectancy of the diabetic was referred to enthusiastically by Joslin when he stated that he had recently seen an advertisement of a life insurance company headed as follows: "Controlled diabetics are now eligible for life insurance."

In figure 54-1 the statistics in diabetes are shown, which present an optimistic view. Joslin shows the proportion of fatal cases of diabetes surviving 20 years or longer in different eras.

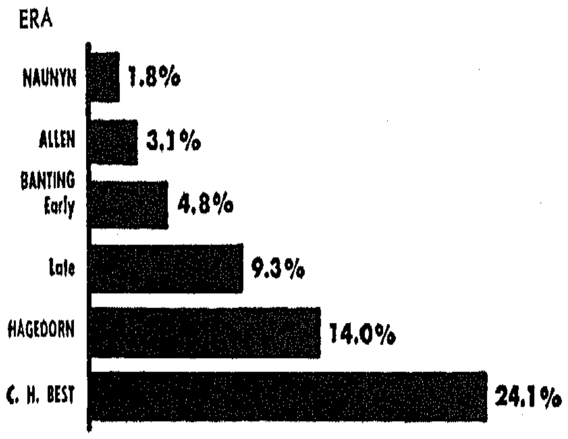


FIG. 54-1. Proportion of fatal cases surviving twenty years or longer. Data based on 10,673 fatal cases reported to April 27, 1949.

Diabetes is a very prevalent disease. Present estimates based on a number of recent surveys of population samples are that there are 1.5 million diabetics in the United States and another 1.4 million undiagnosed cases. The actual incidence in the United States appears to be about 2 per cent. Despite the use of insulin the disease ranks high among the causes of death. However, in evaluating mortality statistics on controlled diabetics, it is important to know whether the death occurred "of" diabetes or "with" diabetes owing to some other factor.

The disease appears to exhibit an hereditary tendency. The trait of the predisposition to diabetes suggests the unwisdom of intermarriage among diabetics. Also, it may be unwise for non-diabetics to intermarry if each family has a history of diabetes. The physician should warn that should marriage in these categories occur the offspring should be induced to take measures to minimize the inherent diabetic hereditary susceptibility.

The incidence is high among the obese and sedentary workers under emotional strain. The Hebrew male appears to possess a special susceptibility to the disease. In the African Negro native the disease is seldom encountered. However, some authorities contend that the incidence of diabetes is nearly uniform in all races if data are based upon adequate study.

**Some considerations of diabetes mellitus.** The discovery of the production of diabetes by Dunn *et al.* (1943) by the injection of alloxan has stimulated much interest in the etiology of the disease. Alloxan is mesoxalylurea. The close chemical relationship of this compound to products of metabolism such as uric acid and urea suggested the possibility of diabetes resulting from a biochemical lesion in muscle, producing alloxan.

There appear now to be 4 types of diabetes that can be produced in animals. These are:

1. Surgical diabetes (partial or total pancreatectomy)
2. Endocrine diabetes (produced by anterior pituitary extracts, especially the growth hormone)
3. Alloxan diabetes
4. Over-alimentation diabetes (produced by continuous injection of dextrose in cats)

Between the first 2 types of diabetes there are many similarities and few differences. But both differ in many respects from the chemical diabetes produced by alloxan.

The hydropic degeneration of the beta cells of the pancreas produced by partial pancreatectomy appears to be identical with that produced by the anterior pituitary diabetogenic hormone. The change is at first reversible and later becomes permanent. In alloxan diabetes these cells from the very beginning show degenerative changes that lead to necrosis. They do not show the hydropic appearance as a first effect.

The study of the histopathology of alloxan diabetes has shed light upon the possible function of the *alpha* cells in the islet tissue. Thorogood and Zimmerman (1945) showed that when dogs with alloxan diabetes were depancreatized, their insulin requirements diminished. This has been noted in human beings with diabetes who have been depancreatized. It has been suggested that the alpha cells secrete a glycogenolytic hormone which antagonizes the action of insulin. Heard *et al.* (1948) reported studies which indicated the existence of such a hormone.

The hyperglycemic factor *glucagon* has been known to be present in most insulin preparations for more than 40 years (Piper, 1923, and others). It has been isolated and purified in crystalline form by Staub and others (1953). The crystals contain only traces of zinc. Bromer *et al.* (1956) studied the structure of glucagon and showed it to be a protein consisting of 29 amino acid units. The 15 different amino acids are linked in a single chain in the molecule. The sequence of the amino acid chain has been determined. Biologic activity of the crystalline material is such that after intravenous injection, 0.1 μg. of glucagon/kg. produces a 30-mg. rise in blood sugar level of the cat. Kirtley *et al.* (1953), in studies of the effect of glucagon on human diabetics, observed different types of responses in the blood sugar and inorganic phosphorus of stable and unstable patients. In contrast to the stable cases, the latter had a normal fall in serum phosphorus. The role of glucagon in human diabetes has not yet been determined.

It is clear that glucagon is not a factor indispensable to carbohydrate metabolism. However, insulin sensitivity and susceptibility to ketosis appear to be aggravated in animals and man after pancreatectomy more than in other forms of diabetes.

Glucagon stimulates hepatic glycogenolysis by increasing the concentration of 3′,5′-cyclic adenosine monophosphate which then stimulates the conversion of inactive phosphorylase to active phosphorylase in the liver. Although the most obvious action of glucagon is the production of hyperglycemia, there is growing evidence that this hormone may also play a significant role in the regulation of lipid and protein metabolism.

Salter (1960) injected rats repeatedly over several days with glucagon. They suffered weight loss, synthesized less protein and fat, and upon sacrifice at the end of the treatment there was a reduced insulin content of the pancreas. It is clear that this hormone exerts a significant effect on caloric balance.

At present glucagon is being successfully used to terminate insulin-induced coma when this measure is used in the treatment of mentally ill patients and also to treat insulin reactions in diabetes, especially the juvenile type. In the latter case the dose is usually 1 mg. subcutaneously (Elrick *et al.* 1959).

The fact that not all normal persons are susceptible to the diabetogenic effect of ACTH (Conn, 1950) may have broad implications with respect to diabetes susceptibility and its hereditary aspect. Persons susceptible to the diabetogenic effect of ACTH are also similarly susceptible to cortisone. This major difference in individuals may lie in the end-organ response to "11-oxysteroid" activity rather than to differences in adrenal-steroid production, and probably involves, at the enzyme level, decreased insulin production and/or cellular resistance to the physiologic effects of insulin.

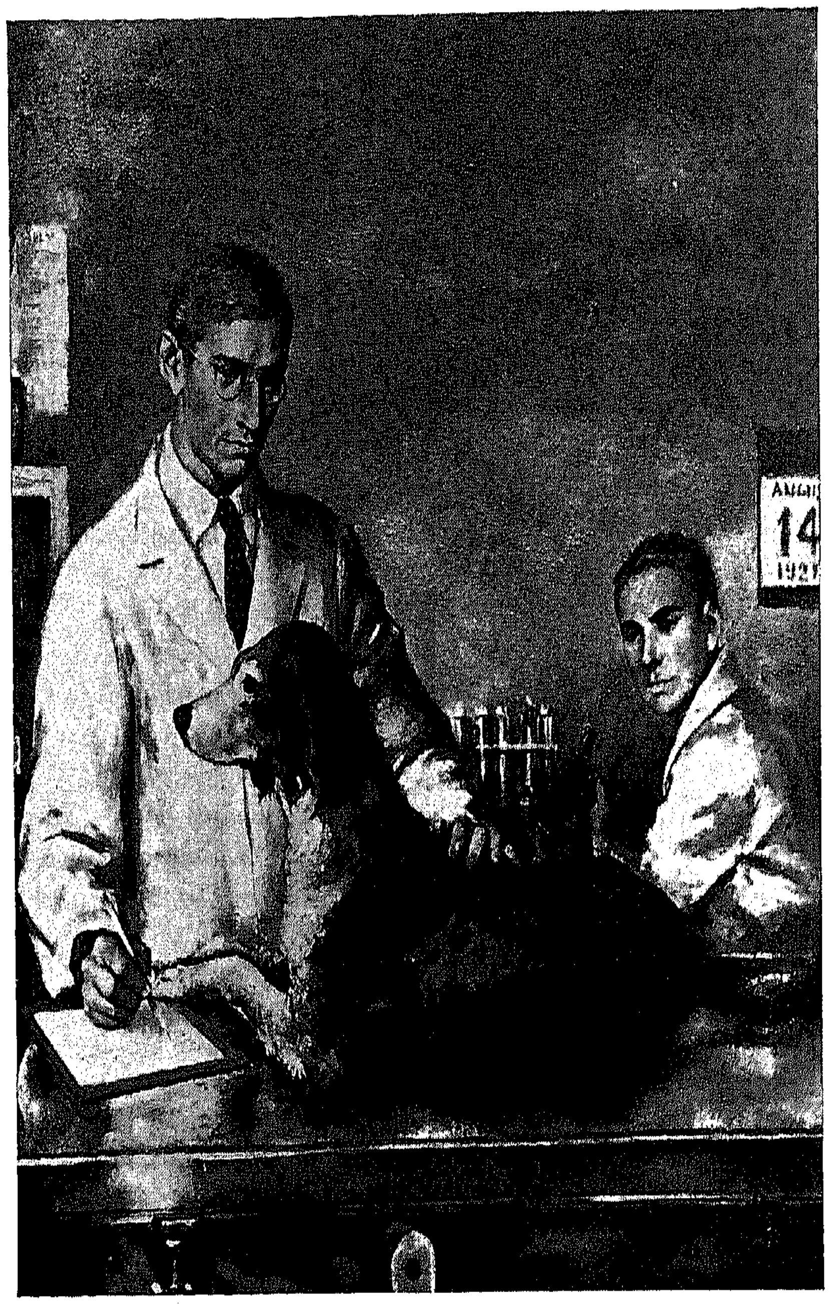
Since the discovery of insulinase and insulinase-inhibitor in liver (Mirsky and Perisutti, 1955), other factors possibly involved in diabetes present themselves. Thus, a plethora of insulinase or a deficiency of insulinase-inhibitor or both could be important factors in the etiology of the disease.

Other factors which may play a role in either the development or progress of diabetes are several insulin inhibitors which have been found in the sera of patients with diabetes who are resistant to the normal action of insulin. One of these factors is synalbumin, which Vallance-Owen (1960) has discovered and which appears to be made up of the B-chain of insulin combined in some fashion with serum albumin. Present evidence indicates that this factor is probably genetically determined and may account for the fact that a tendency to diabetes is inherited.

**The discovery of insulin.** There is no more dramatic episode in the annals of medical research than the discovery of insulin. For the knowledge and inspiration to be gained from this epoch-making research several paragraphs are quoted from an address by Sir Frederick G. Banting in 1934.

"To go back to July, 1920, after spending four years' post-graduate work in surgery at military and civilian hospitals, I commenced the practice of medicine in London, Ontario. After I had observed the conventional office hours of 2 to 4 p.m. and 6 to 8 p.m. for twenty-eight consecutive days, my first patient presented himself. At the end of the month I had four dollars on the books. The succeeding months were not much more gratifying. However, in October, when the medical school opened, I was successful in obtaining an appointment as demonstrator in the Departments of Physiology and Anatomy which gave me access to these laboratories. On the 30th of October, it so happened that in the early part of the evening I was preparing a lecture on the relation of the pancreas to diabetes, and when the lecture was completed I commenced the perusal of the newly arrived November number of *Surgery, Gynecology and Obstetrics*. This journal contained an article by Moses Barron in which he pointed out the analogy between the degenerative changes which follow the experimental ligation of the pancreatic duct, and the blockage of the duct by gallstones.

"After reading the article by Barron I was unable to sleep. There seemed to be in some vague way a relation between the islet cells of the pancreas and clinical diabetes. There seemed also to be a means of attacking the problem of extracting the islet cells by ligating the pancreatic duct. It was not until two o'clock in the morning that I



DRS. BANTING AND BEST IN THE LABORATORY

“An extract was made in the usual way and carefully administered intravenously to a depancreatized dog on 19th November, 1921. Following the injection the blood sugar fell from 330 mg. per cent to 170 mg. per cent in one hour.” (By permission of Eli Lilly and Company.)

was able to crystallize the idea into a form that would lend itself to experimentation. At this hour I arose and wrote in my notebook the following words: ‘Ligate pancreatic ducts of dogs. Wait six to eight weeks for degeneration. Remove the residue and extract.’ The following morning I consulted a number of the professors at London concerning the idea, and inquired as to the possibilities of obtaining facilities for experimental work. Unfortunately, it so happened that since the new medical school was not completed, facilities and assistance could not be provided. On the advice of Professor Miller, I went to the University of Toronto, my Alma Mater, to consult Professor J. J. R. Macleod. I had never met Professor Macleod until this time, but his reputation as an authority on carbohydrate metabolism was well known.

“Work was commenced on the 16th of May, 1921. It was arranged that I should have ten dogs and the use of the laboratory for eight weeks. Mr. Best and Mr. Noble were appointed as assistants, each to give four weeks. They tossed a coin to decide who would give the first four weeks, and Mr. Best won the toss. At the end of the four weeks, however, Mr. Noble did not return and Mr. Best stayed with me and was associated with me throughout the entire work.

“We first ligated the pancreatic duct of a number of dogs. Following this we did a number of pancreatectomies in normal dogs to familiarize ourselves with the blood and urinary findings and the general clinical behavior of the dogs following this operation.

“On 27th July, 1921, we had a depancreatized dog and we decided to begin treatment. A duct-tied dog was chloroformed and the degenerated residue was removed. It was chopped into small pieces in a chilled mortar and frozen in brine. The mass was ground up and about 100 cc. saline were added. Five cc. of this extract were administered intravenously into the depancreatized dog. Samples of blood were taken at half-hour intervals and showed that the blood sugar had fallen from 0.200 to 0.11 per cent in two hours. The clinical condition of the dog was markedly improved.

“An extract was made in the usual way and carefully administered intravenously to a depancreatized dog on 19th November, 1921. Following the injection the blood sugar fell from 0.33 to 0.17 per cent in one hour. This result was confirmed by subsequent injections. We were thus able to maintain an adequate supply of the active principle of the islands of Langerhans with no expense to the laboratory, and in quantities which provided for repeated trials and various extractions. It was found that the active principle could be extracted from the fetal gland with acetone and alcohol, and that it was not destroyed by chloroform or ether.

“On 11th January, 1922, the first patients were treated with extract in the Toronto General Hospital. Following the injections there was a typical lowering of blood sugar and a slight decrease of the sugar in the urine. But since the percentage of protein in the extracts was high, a sterile abscess developed at the point of injection.

“Our results in the human were, however, sufficiently encouraging to change the whole trend of the research. Professor J. J. R. Macleod abandoned his work on anoxemia and turned almost his whole laboratory staff to the problem of the physiological activity of this pancreatic extract.

“Insulin was not the first name used among our group of workers. As early as August, 1921, the word ‘isletin’ occurs in our notebooks. Professor Macleod insisted that the internal secretion of the pancreas should be called ‘insulin.’ Later it was found that Sharpey-Schafer of Edinburgh suggested this name about 1910.

“During the spring of 1922, Dr. Best succeeded in producing quantities of insulin sufficiently large and sufficiently purified to prove thoroughly the value of insulin to diabetic patients. A large number of hopeless severe diabetics began to come to Toronto. It was the ideal of all those associated in the work to obtain the largest quantities of insulin at the lowest possible price for the rapidly increasing clinical needs.”

**Preparation of insulin.** Insulin is prepared for medicinal purposes by the extraction of minced pancreas with acidulated dilute alcohol. Purification is effected by fractional precipitation with higher alcoholic concentrations, isoelectric precipitation, salting out the hormone, or its separation in the form of an insoluble salt. Nearly all of the commercially available insulin is prepared from the pancreas of beef or pig. The official insulin injection is a highly-purified preparation of the hormone. The solution is acid, pH 2.5 to 3.5, and quite free from foreign protein.

**Crystalline insulin.** When Abel (1926) first prepared crystalline insulin no physiologically active protein was known. It is not surprising, then, that lively debate occurred as to whether the hypoglycemic action was due to the crystalline material or to another, perhaps smaller, entity adsorbed on the crystals. Subsequent work has demonstrated adequately that the hormone can be obtained as a crystalline protein. Now that many potent physiologic agents have been isolated as crystalline proteins, such materials are accepted as a matter of course.

In 1934 Scott made the observation that all crystalline insulin samples contained small amounts of heavy metals such as zinc, cadmium, nickel, or cobalt. He found that insulin solutions completely free of these metals would not crystallize. Crystallographic studies have shown that these heavy metals do not occur as impurities in the crystals, but are actually an integral portion of the crystalline structure. Recent experiments suggest that one zinc ion is bound to 2 imidazole groups of adjacent subunits of 12,000 molecular weight.

Crystallization of insulin occurs when the pH of highly purified amorphous insulin in a zinc ion containing buffer is adjusted to a value close to the isoelectric point of the protein; the average zinc content of crystals obtained is 0.4 per cent.

A more recent modification of insulin crystallization will yield crystals containing 2 per cent of zinc or more by using an acetate buffer at pH 7.0 with an excess of zinc ions. These preparations have decreased solubility and are of practical importance because of their delayed biologic action. These are the properties which are utilized in the “Lente” and “Semi-Lente” insulin modifications.

Crystalline insulin is readily soluble in dilute acid and alkali, but is nearly insoluble from pH 4.5 to 7.0. The isoelectric point of the protein is 5.30 to 5.35. As previously mentioned, the type and amount of certain cations and anions greatly influence the solubility of insulin, especially in the region of its isoelectric point.

**Structure of the insulin molecule.** Much effort has been spent on attempts to correlate the physiologic activity of insulin with specific parts of the molecule or with various functional groups.

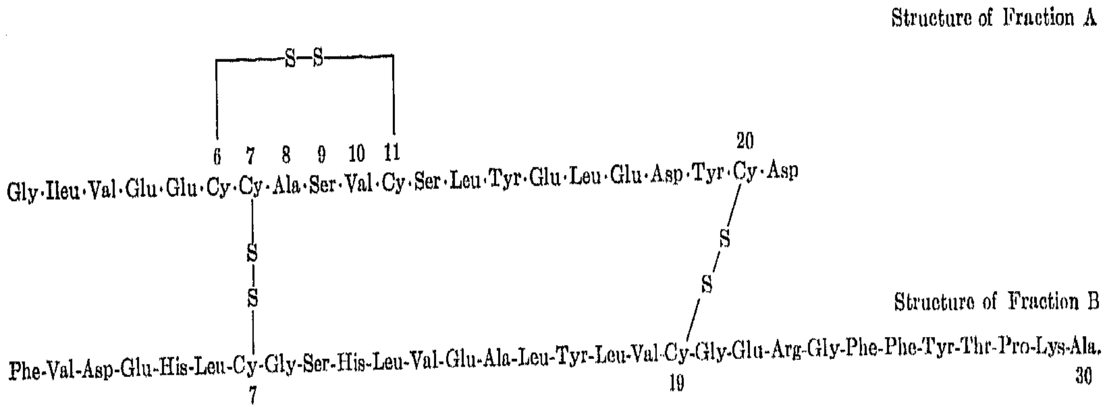

Structure of Fraction A
S—S
6 7 8 9 10 11
20
Gly·Ileu·Val·Glu·Glu·Cy·Cy·Ala·Ser·Val·Cy·Ser·Leu·Tyr·Glu·Leu·Glu·Asp·Tyr·Cy·Asp
S
S
S
S
Structure of Fraction B
Phe-Val-Asp-Glu-His-Leu-Cy-Gly-Ser-His-Leu-Val-Glu-Ala-Leu-Tyr-Leu-Val-Cy-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-Ala.
7
19
30

FIG. 54-2. S—S linked structure for insulin (beef). Katsoyannis *et al.* (1963) have synthesized both the A and B chains of insulin, and Dixon and Wardlaw have been able to combine these two synthetic chains and produce a biologically active molecule. The yield for these synthetic reactions is low and only minute quantities of synthetic insulin have been prepared. (From F. Sanger, Biochem. J., **45:** 563, 1949).

Determination of the chemical composition and elucidation of the structure, especially of physiologically active proteins, are among the foremost problems of advanced protein chemistry. Such problems require that the protein studied be of high purity. Crystallinity of a protein is not a valid criterion of purity. To gain conclusive information in this regard, the protein must be studied and characterized by many physicochemical, chemical, and biologic methods.

It has been shown that the insulin from beef, pork, and sheep differs in its amino acid composition. Earlier reports had suggested that there were significant quantitative and probably even qualitative differences in amino acid composition in insulin preparations from different species.

Sanger (1949) succeeded in oxidizing insulin with performic acid and was able to separate the oxidation product into 2 fractions. He named these fractions A and B and was able to demonstrate that they corresponded to 2 straight polypeptide chains which were linked together in the intact insulin molecule by disulfide bridges.

The amino acid sequence of the A and B chains of the insulin molecule are shown in figure 54-2.

**The administration of insulin.** From the very earliest days of insulin therapy the hormone has been administered by subcutaneous injection. In emergencies it may be given intravenously. The subcutaneous injection of insulin is a satisfactory method of administration in nearly all diabetics, except for the discomfort of repetitious hypodermic injections.

Undoubtedly the most satisfactory method of administration of insulin for the convenience and comfort of the patient would be orally. This has never been achieved satisfactorily. There have been some oral substitutes marketed in this country and in Europe, but their value when subjected to rigorous examination has been found worthless. Insulin as a protein molecule is attacked by enzymes of the gastrointestinal tract. If this were the only difficulty it could obviously be overcome by the use of enteric coated capsules or pills. But the problem is more fundamental. The molecule as such is not absorbed from the intact intestinal mucosa.

Bollman and Mann (1932) exteriorized a loop of a dog's intestine. The lumen was exposed over a small area and washed free of enzymes. Insulin solution was applied to the exposed intestinal mucosa. The blood sugar levels were taken at short intervals. No hypoglycemia was evoked. A small quantity of insulin was then injected submucously. The blood sugar level fell precipitously, and hypoglycemia was immediately obtained.

From time to time there have been efforts made to cause insulin to pass through the intestinal tract with the aid of surface tension reducing agents. The outlook for an oral insulin preparation is not favorable. With the use of longer-acting insulins and the oral hypoglycemic drugs, the urgency for an oral insulin product is not so pressing as it was formerly.

**The role of insulin in carbohydrate metabolism.** From the point of view of clinical medicine the most satisfactory picture of the effect of insulin on carbohydrate metabolism is seen by reviewing the cardinal biochemical lesions and symptoms of diabetes. By depancreatizing an animal or in diabetes that occurs in human beings, the insulin insufficiency manifests itself in the following manner:

1. Hyperglycemia and glycosuria
2. Depletion of glycogen stores in the liver and tissues

3. Lowered respiratory quotient indicating the lack of carbohydrate oxidation
4. Increase in urinary nitrogen excretion indicative of the conversion of protein into carbohydrate
5. The occurrence of acetone and betahydroxybutyric acid in the blood and urine owing to faulty fat metabolism

At a cellular level the possible mechanisms of the defects in carbohydrate metabolism are shown schematically in figure 54-3.

The injection of insulin will relieve these symptoms and restore to normalcy the distorted metabolic pattern. In the main, insulin will facilitate the oxidation of glucose, cause glycogen to be stored in the liver, and enable the conversion of glucose to fat.

As the diabetic utilizes more fat to compensate for the reduced glucose metabolism, endogenous fat is metabolized and weight loss occurs. The synthesis of fat is also impaired. In the normal individual about 30 per cent of the ingested carbohydrate is converted to fat; in the diabetic only about 5 per cent of carbohydrate is converted to fat. Thus, the lipid metabolic defect has 2 components, excessive breakdown of fatty acids leading to ketosis and acidosis and the impairment of fat synthesis from carbohydrate. A major defect occurs as shown in figure 54-3 in the failure of the diabetic organism to convert acetyl-coenzyme A into long chain fatty acids.

Liver slices from alloxan-diabetic rats were shown to be incapable of synthesizing fatty acids from glucose, fructose, lactate, pyruvate, or acetate. Each substance, except glucose, was converted into acetyl-coenzyme A, but further synthesis of the long chain fatty acid did not occur. Thus, it appears that insulin is necessary for the hexokinase reaction in the case of glucose as shown in figure 54-3.

Levine and his associates (1949 *et seq.*) considered the possibility of insulin's exerting its primary effect on some fine structure of the organized cell surface. To demonstrate this possibility they used galactose in the eviscerated, nephrectomized dog and rat. In these test objects galactose is not metabolized and can be quantitatively reecovered from the carcass. In these animals the administration of insulin facilitated the entrance of galactose to the muscle cells, as shown by its disappearance from the blood. The fact that insulin exerts its usual action on a substance which is not utilized by the tissues suggests that it does not act upon the cellular enzyme systems. Stadie *et al.* (1949) also demonstrated that other hormones affected the influence of insulin on the permeability of the cell membrane. It appears that insulin influences the permeability of the cell membrane, permitting the entrance of glucose, which in turn is degraded by the enzyme systems of the cells.

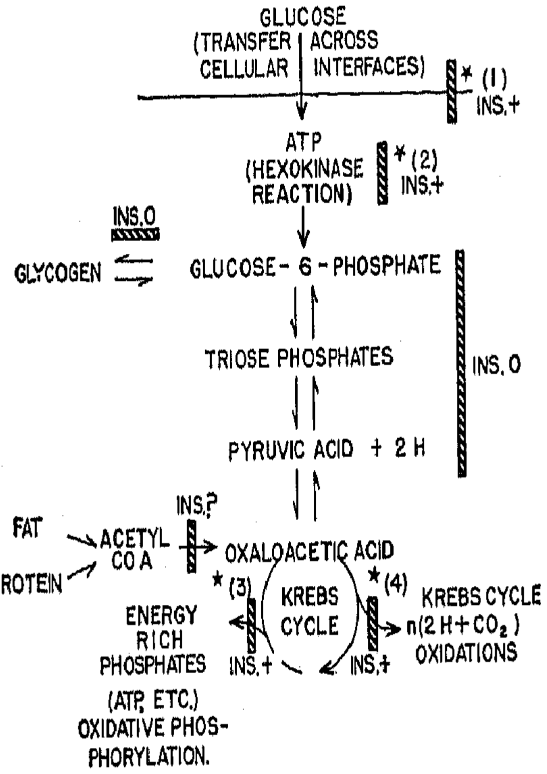


FIG. 54-3. Current schema of glycolytic and Krebs cycles. Possible "metabolic defects" associated with insulin deficiency are indicated by *hatched blocks:* (1) glucose transfer, (2) hexokinase reaction, (3) oxidative phosphorylation and (4) oxidative reactions in Krebs cycle. (From W. C. Stadie: Am. J. M. Sc., **229:** 223, 1955).

Wick *et al.* (1951) confirmed the action of insulin in facilitating the diffusion of glucose into cells by means of $C^{14}$-labeled hexoses. Using $C^{14}$-labeled galactose in experiments similar to those of Levine previously described, Wick found the entrance of galactose into the cell markedly accelerated by insulin. Wick stated, "Galactose does not get into the cells by diffusion but must be forced into the cells by some chemical process analogous to a pumping mechanism that is accelerated by insulin. We can conclude that insulin acts on glucose in the same way."

Levine and Goldstein (1953) studied the effect of insulin on the transfer of sugars across cell barriers. Insulin appeared to promote the entry into cells of such sugars which possess the same chemical configuration at carbon atoms 1, 2 and 3 as does *d*-glucose. This action of insulin is independent of any subsequent utilization of the sugar within the cell. Levine and Goldstein hold the view that there exists at the surface of certain cells a barrier which opposes the entry of sugars. Insulin, on the other hand, facilitates a transport system capable of carrying sugars of a definite chemical structure into the interior of the cell. Thus, the metabolic effects of insulin appear to be dependent upon a more rapid rate of entry of glucose into the cell.

Additional evidence of the action of insulin on cell surfaces was presented by Stadie *et al.* (1952). They showed that rat diaphragm immersed momentarily in insulin solution and then equilibrated with glucose synthesized a far greater amount of glycogen than the tissue not exposed to insulin. Using insulin tagged with $I^{131}$ they showed that the insulin molecule combined firmly with the tissue and resisted the dissociating action of washing. It was found that the metabolic activity of insulin, *i.e.*, uptake of glucose and synthesis of glycogen, was proportional to the amount of insulin so bound by the diaphragm.

From the data in figure 54-3 it is evident that phosphorylation plays an important role in the oxidation of glucose. Price *et al.* (1945) reported that extracts from the anterior lobe of the pituitary antagonized the transformation of glucose to glucose-6-phosphate. This antagonism is opposed by insulin. This is the first step in glucose metabolism, and insulin may exert its effect in the control of glucose breakdown by influencing favorably the phosphorylation process. Apparently the anterior lobe principle inhibits the action of hexokinase in its role of the phosphorylation of glucose to glucose-6-phosphate at the expense of adenosine triphosphate. The use of ACTH in rheumatic fever and other diseases has repeatedly verified the diabetogenic potentialities of this pituitary hormone. This concept is confirmed by the finding that the administration of glucose and insulin to rabbits results in an increase in hexose phosphates of muscle. Hall (1954) demonstrated that insulin enhanced the oxygen uptake of muscle slices from diabetic rabbits by more than 60 per cent. It had no potentiating action on the muscle of normal rabbits.

Miller *et al.* (1956) studied the metabolism of fructose in normal and diabetic subjects when the hexose was administered intravenously. When fructose is given intravenously to a diabetic without insulin, there is a large and rapid increase in the pyruvate in the blood. When glucose is given, pyruvate appears in the blood in small amounts and slowly. This is interpreted to mean that the diabetic can metabolize fructose similarly to a normal person. By means of hepatic vein catheterization studies, it was shown that the liver of the diabetic was able to convert fructose to pyruvate similarly to that of a normal person. Ketosis when present, however, retarded the metabolism of fructose by the diabetic liver. These studies elucidate further the metabolic defect in the diabetic. Fructose enters the scheme (see figure 54-3) after the phosphorylation of glucose. It appears that the principal features of the metabolism are its almost exclusive utilization by the liver and its independence of insulin in its metabolic processes (Renold and Thorn, 1955). Therefore, it is apparent from these studies that the aberration is at the point of glucose phosphorylation. This is accomplished by hexokinase. In the diabetic this process is impaired.

The protein loss in the diabetic results from the inordinate breakdown of amino acids to form glucose (gluconeogenesis) and from the failure of the diabetic organism to synthesize protein. Protein synthesis is decreased in the liver and muscle in the absence of insulin. Krahl (1956) showed that the conversion of radioactive glycine into the tripeptide glutathione took place to a very limited degree in slices of the liver of the fasted diabetic rat. The addition of glucose enhanced the synthesis of glutathione. The addition of glucose plus insulin further increased peptid synthesis to nearly the normal rate. Thus it has been established that the anabolic and catabolic processes of the 3 essential food constituents (carbohydrate, fat, and protein) are insulin-dependent.

The role of insulin, therefore, appears to be as follows: (1) it facilitates the passage of glucose through cell barriers into the cell; (2) it effects the phosphorylation of glucose; insulin also plays a role in oxidative phosphorylation; and (4) it is essential to lipid and protein catabolism and anabolism. The role of insulin in the treatment of diabetes is shown schematically in figure 54-4.

### INSULIN IN THE TREATMENT OF DIABETES

Not all cases of diabetes require insulin. Mild diabetes in the older person may be controlled by dietary regulation alone. Nevertheless, not all cases are "mild" in the aged, for some of them become acidotic rapidly if insulin is withdrawn. The patient is usually hospitalized and placed on a maintenance diet providing sufficient calories

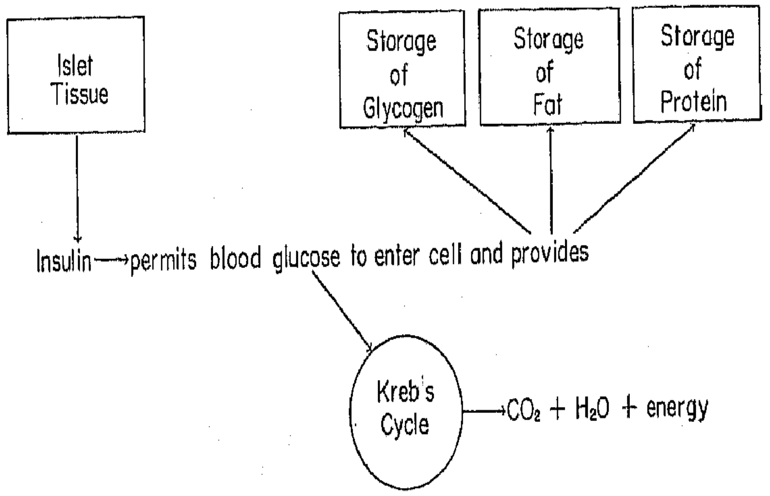

Islet Tissue
Storage of Glycogen
Storage of Fat
Storage of Protein
Insulin→permits blood glucose to enter cell and provides
Kreb's Cycle
→$CO_2$ + $H_2O$ + energy

FIG. 54-4. Schematic role of insulin in metabolism. In diabetes the entrance of glucose into the cell is inhibited. The blood sugar level is increased, and energy requirements are met by depleting the stores of glycogen, fat, and protein. Ketone, acetoacetate, and $\beta$-hydroxybutyric acid are formed mainly by the liver as the result of excessive fat metabolism and increased production of acetylcoenzyme A. Since fatty acid synthesis is blocked, acetylcoenzyme A is disposed of by conversion to acetoacetate and cholesterol.

for moderate activity. If under these conditions the person becomes aglycosuric and the blood sugar level returns to nearly a normal value, insulin is not indicated. However, such cases of diabetes controlled by diet alone will likely require insulin should any infection occur. Infections in general diminish carbohydrate tolerance. Thus, there are 2 main indications for insulin. Insulin should be used in any case where the normal state of nutrition cannot be maintained and secondly, in any case where a complication such as infection or acidosis exists. Nearly all juvenile diabetics need insulin.

If on a maintenance diet the patient excretes glucose, insulin is indicated. A convenient method of transformation of the laboratory standardized unit on the rabbit to the human diabetic is as follows. The average daily excretion of dextrose is determined. This value divided by 1.5 will express the usual daily dose of insulin in units required to render the individual aglycosuric. Thus, if 45 gm. of dextrose is found on the average in the urine daily on a maintenance diet, 30 units (45/1.5) of insulin are indicated. There is, however, considerable variation in the amounts required.

One dose of 20 units is given about 30 minutes before breakfast, and the smaller, or 10-unit dose, is administered 30 minutes before the evening meal. Some rearrangement in the quantities of food at different meals may be advantageous. Carbohydrate tolerance is usually at its lowest ebb in the morning, and progressively larger meals may sometimes be given at lunch and dinner without necessitating any increase in dosage of insulin.

In more severe cases of diabetes, unmodified insulin is required 3 or even 4 times daily. In these instances a dose of one of the modified long-acting insulin preparations each day is the cornerstone of insulin therapy.

**Hypoglycemic shock.** One of the hazards of insulin administration is the production of hypoglycemic shock. This phenomenon was observed by Banting *et al.* (1922) in their early experiments with pancreatic extracts on dogs. The hypoglycemic symptoms which occur in man are *hyperirritability*, *trembling*, *incoordination*, *muscular weakness*, *disorientation*, *convulsions*, *unconsciousness*, and *death*.

There have been many theories proposed to account for hypoglycemic shock. Its production in laboratory animals has made the phenomenon amenable to careful study. Rabbits generally show shock symptoms when the blood sugar level is 45 mg. per cent. Dogs are very resistant and show symptoms when the blood sugar level is in the region of 18 mg. per cent. Pigeons have a normal blood sugar level of 160 mg. per cent and do not show shock symptoms when the concentration of sugar is reduced to 80 mg. per cent.

Hypoglycemic shock occurs in animals after the destruction of the cerebral hemispheres, but not after the medulla has been destroyed. The respiratory quotient of the brain tissue is unity. Glucose is the primary fuel. The removal of the sugar from the circulating blood is comparable to the abolition of its necessary substrate. Without substrate, oxidation cannot continue. One produces a condition comparable to anoxia but in the presence of sufficient oxygen. The insulin convulsion has been considered in the same category as convulsions produced by cyanide poisoning which interferes with the oxygen uptake by brain cells.

In normal persons hypoglycemic shock occurs at a much lower state of glycemia than in diabetics. In the diabetic with a constantly persisting hyperglycemia, symptoms of shock may occur if the blood sugar level is *suddenly* brought down to 80 to 90 mg. per cent. Rabinowitch *et al.* (1937) observed patients using protamine-zinc insulin with very low blood sugar levels for long time periods without symptoms. He attributed this to the slowness of the onset of the lowering of the blood sugar level. Indeed, it appears that the rapidity of production of hypoglycemia is an important factor in the appearance of symptoms.

The symptoms of hypoglycemia are readily relieved by the administration of *soluble carbohydrate.* Orange juice, dextrose solution, or sucrose administered orally are effective. If the shock is severe, dextrose solution may be administered intravenously. Symptoms of shock often occur very suddenly. It is therefore advisable for the patient using insulin to have available at all times a convenient supply of soluble carbohydrate. Patients who are taking any long-acting insulin preparation may require retreatment for hypoglycemia at intervals over several hours, and they should be kept under close observation for a few days until satisfactory readjustment of insulin dose and diet has been successfully accomplished.

Epinephrine injection, 1–1000, 0.5 ml. subcutaneously, has been used in the treatment of hypoglycemic shock. Its value is dependent upon the availability of glycogen in the liver for mobilization as glucose. Generally, this condition does not obtain in the diabetic, and epinephrine should be used only in emergencies when intravenous glucose is not on hand and the oral administration of soluble carbohydrate is not available. If epinephrine is administered, it should be followed by carbohydrate.

Glucagon is more effective than epinephrine for the treatment of hypoglycemic shock. A dose of 1 to 2 mg. subcutaneously or intramuscularly will usually increase blood glucose sufficiently to restore consciousness. Once the patient is able to respond, carbohydrate must be given by mouth as the response to glucagon is of short duration. There are no side effects produced by glucagon in the dose used to treat hypoglycemic reactions, and even a large overdose is not toxic.

**Insulin requirements.** In a foregoing paragraph it was mentioned that the presence of infection diminished the tolerance for carbohydrate of the diabetic and therefore required additional insulin. In practice the physician will observe that even a slight infection of the throat will often produce hyperglycemia in an otherwise well-controlled diabetic. It has been shown that injured cells, as manifested by inflammation, in diabetic and nondiabetic animals are characterized by an increase in their protein catabolic processes and by becoming potential sites of *gluconeogenesis.* In the normal organism the extra sugar is of no consequence; in the diabetic, however, the delicately balanced metabolic pattern of carbohydrate metabolism is distorted.

The effect of damaging stimuli (stress) in relation to homeostatic regulation of carbohydrate metabolism has been elaborated on by Selye in connection with his concept of the adaptation syndrome.

Ricketts *et al.* (1945) completely depancreatized a nondiabetic man with a pancreatic malignancy. After the operation the diabetes was controlled with 30 to 50 units of insulin daily. Diabetics requiring greater quantities of insulin probably have their disease complicated by extra pancreatic factors, possibly of pituitary or enzymic origin. Yalow and Berson (1960) estimated by means of metabolic studies with insulin $I^{131}$ that average secretion of insulin in the normal male is 55 units daily.

Others have reported cases of total pancreatectomy in human beings and have been impressed by the mildness of the diabetes which resulted from this procedure. However, these patients have also lost the external secretion of the pancreas and are unable to absorb food normally. Consequently, they are usually in a state of severe inanition. Under such circumstances not much insulin is needed.

Bornstein (1950) developed an insulin assay utilizing the alloxan-diabetic, hypophysectomized, adrenalectomized rat. In a brilliant series of investigations he determined the insulin concentration in normal man and in cases of human diabetes. His method gave consistent and similar results to those of Willebrands and Groen (1954) who used the isolated rat diaphragm. The normal blood insulin was found to be 100 $\mu$U./ml. Many diabetic persons were found to have a relatively high level of blood insulin, indicating the possibility of the presence of some unknown inhibitor of insulin action.

However, more recent studies using the rat epididymal fat pad as an assay system or the radio-immunoassay developed by Berson and Yalow have given quite different values for circulating serum insulin, and this question is again in a state of controversy. Using the rat diaphragm as the assay system, the circulating serum insulin concentration in normal man is found to be 60 to 100 $\mu$U./ml.; normal values for the fat pad assay average around 200 $\mu$U./ml.; and in the radio-immunoassay normal values average 20 to 25 $\mu$U./ml. All 3 of these assays show increases in insulin concentration when glucose is administered, and all 3 assays have shown that many diabetic persons have a relatively high level of circulating insulin. It is thus possible to conclude that such diabetics have some type of inhibitor of insulin action even though it is not possible to be definite about the absolute amount of insulin in the circulation.

In the routine administration of insulin it is a common observation that with a low dosage the amount of carbohydrate oxidized by 1 unit of insulin is about 1.5 gm. However, if the amount of carbohydrate in the diet is increased, the efficiency of insulin is increased to 2 or even 3 gm. of carbohydrate per unit of the hormone. This is a common practice in the treatment of diabetes, namely, to permit a relative abundance of carbohydrate, 150 to 200 gm. daily, and to compensate for it with additional insulin. High blood levels of fat are thereby diminished and early atheromatous deposits in the walls of the blood vessels are thought to be retarded. Besides, a high carbohydrate diet is inexpensive, pleasant to ingest, and provides an excellent source of energy. Furthermore, the danger of acidosis is almost completely averted.

Cases of diabetes refractory to insulin have been mentioned. Undoubtedly many of these cases show a distinct humoral antagonism. For example, Smelo (1947) recorded a diabetic who took upwards of 3000 units of insulin per day to control the disease. However, in some cases using insulin with a radioactive zinc atom it was shown that the resistance to insulin was due to failure of absorption from the depot of injection.

In still other cases the apparent refractoriness is due to the development of antibodies to insulin. Berson and Yalow have shown that patients who have been treated with insulin have circulating antibodies which will bind insulin, and it has been shown that antibody-bound insulin is inactive biologically.

Some patients, who require large doses of insulin when treated with insulin of beef origin, respond to much lower doses of insulin from pork pancreas. This may indicate that these patients have developed antibodies to beef insulin which do not react as strongly with pork insulin, or it may indicate that pork insulin, being closer in chemical structure to human insulin, is not as antigenic in man as is beef insulin.

**Metabolism of insulin.** It has been established that insulin is rapidly destroyed in the body. Mirsky and Broh-Kahn (1949) prepared aqueous extracts of various rats' tissues and demonstrated that they were capable of destroying the hypoglycemic activity of insulin. They assigned the name "insulinase" to the factor. The factor appears to have the properties of an enzyme. It is heat-labile and inhibited by sulfhydryl-binding compounds. The enzyme insulinase appears to be relatively specific in catalyzing the hydrolysis of insulin (Mirsky *et al.*, 1955). The activity of insulinase is diminished by fasting the animal and seems to be related to the nutritional state of the animal.

Mirsky and Perisutti (1955) prepared a liver fraction which contained an enzyme which inhibits the action of insulinase. It has been tentatively called *insulinase-inhibitor.* When injected into rats just prior to the injection of insulin, this inhibitor of insulinase markedly increased the hypoglycemic activity of insulin. Thus, it is possible that another defect in the diabetic metabolic pattern is a paucity of the insulinase-inhibitor.

### INSULIN DOSAGE FORMS

**Insulin Injection, U.S.P. (assay and standardization).** "Insulin Injection is an acidified solution of the active principle of the pancreas which affects the metabolism of glucose." Insulin injection is so standardized that each milliliter contains either 40, 80, or 100 United States Pharmacopeia insulin units. The crystalline zinc insulin standard exhibits an activity of 24 units /mg. The effect of insulin on the metabolism of glucose was determined in the early days of insulin by its action on the blood sugar level of the depancreatized dog. This was a difficult and laborious method of assay. The procedure then adopted was the rabbit assay which is now official. The assay depends upon the capacity of the unknown solution of insulin to reduce the blood sugar in a statistically significant number of rabbits. This is compared with the hypoglycemic activity of a solution of known unitage prepared from United States Pharmacopeia Zinc-Insulin Crystals Reference Standard. Cross-over tests on the 2 series of rabbits are also conducted.

The assays are dependable, and in skilled hands with a sufficiently large series of rabbits the unitage of official insulin is assured well within the United States Pharmacopeia tolerance of ±5 per cent of the labeled potency.

The production of hypoglycemic shock in the mouse is also used as a method of testing the potency of insulin. Insulin evokes hypoglycemia in the mouse, which is manifested by postural eccentricities and convulsive seizures. This method is unofficial, but it is capable of a high degree of dependability.

Protamine zinc insulin injection and NPH insulin injection, as well as globin insulin with zinc injection, are also official preparations.

**Prolonging the hypoglycemia of insulin.** One of the major problems in the management of diabetes with insulin is the maintenance of a nearly normal blood sugar level. The control of nocturnal hyperglycemia presented a perplexing difficulty. Many attempts to prolong the action of insulin were made by various workers. The hormone was mixed with lecithin, tannic acid, and other substances to retard its absorption. Not any of these procedures was found useful clinically.

Professor Hagedorn and his associates of Copenhagen (1936) offered an excellent solution to the problem. They demonstrated that when a solution of protamine (a substance prepared from the sperm or mature testes of salmon) is added to a solution of insulin, an insulin-protamine complex is formed at pH 7.2. Upon subcutaneous injection, this substance is slowly absorbed from the depot, and the hypoglycemia extends over many hours.

Scott and Fisher (1936) reported that zinc salts (1 mg. per 500 units) added to insulin prior to combining it with protamine prolonged its action further. It is of interest that magnesium salts decrease the duration of insulin hypoglycemia. Protamine zinc insulin soon became established as a very valuable adjunct to the physician's armamentarium in the management of diabetes.

**Protamine Zinc Insulin Injection, U.S.P.** Protamine zinc insulin injection is a suspension, in a buffered water medium, of insulin modified by the addition of zinc and protamine. The product is available containing 40 or 80 United States Pharmacopeia insulin units in each milliliter.

The major difference in the action of protamine zinc insulin and insulin is simply a matter of time action. The effect of insulin is sudden and profound over 5 or 6 hours, whereas protamine zinc insulin is only slowly absorbed but exerts a hypoglycemic effect for 36 hours or longer.

From these data it is obvious that unmodified insulin produces a very rapid onset of hypoglycemia. It is, however, ephemeral. Protamine zinc insulin, on the other hand, does not produce its maximal effect until 14 to 16 hours after administration, and the over-all duration of action may extend 36 hours or more if large doses are given. It is, therefore, apparent that many individuals would need a morning dose of insulin to provide for breakfast as well as an injection of protamine zinc insulin to keep the blood sugar level down during the remainder of the day and night. This procedure is frequently followed. The overlapping effect into the second day reduces the quantity of insulin needed before breakfast. The disadvantage, however, is the second injection.

This problem was thoroughly investigated by Colwell (1946), and the conclusion was reached after study on many patients that extemporaneously prepared mixtures of the 2 insulins in the syringe provided a solution to the problem. The mixture which Colwell found especially useful was 2 parts of insulin and 1 part protamine zinc insulin.

Many other such quick-acting and long-acting insulin mixtures have been tried. A modification most likely to give good results in a single morning dose is one which releases insulin during the first 12 hours after injection more rapidly than during the second, so that it corresponds to the schedule of daytime feedings and night fasting periods. At 24 hours the action of such a preparation should be strong enough to avoid the necessity of a second daily dose in the evening. It should retain sufficient sustained effect to keep the blood sugar level depressed 24 hours after injection, thus permitting a significant degree of overlapping with the next dose.

**Globin Zinc Insulin Injection, U.S.P.** In 1939 Reiner *et al.* studied the chemical and pharmacologic properties of globin insulin (with zinc).

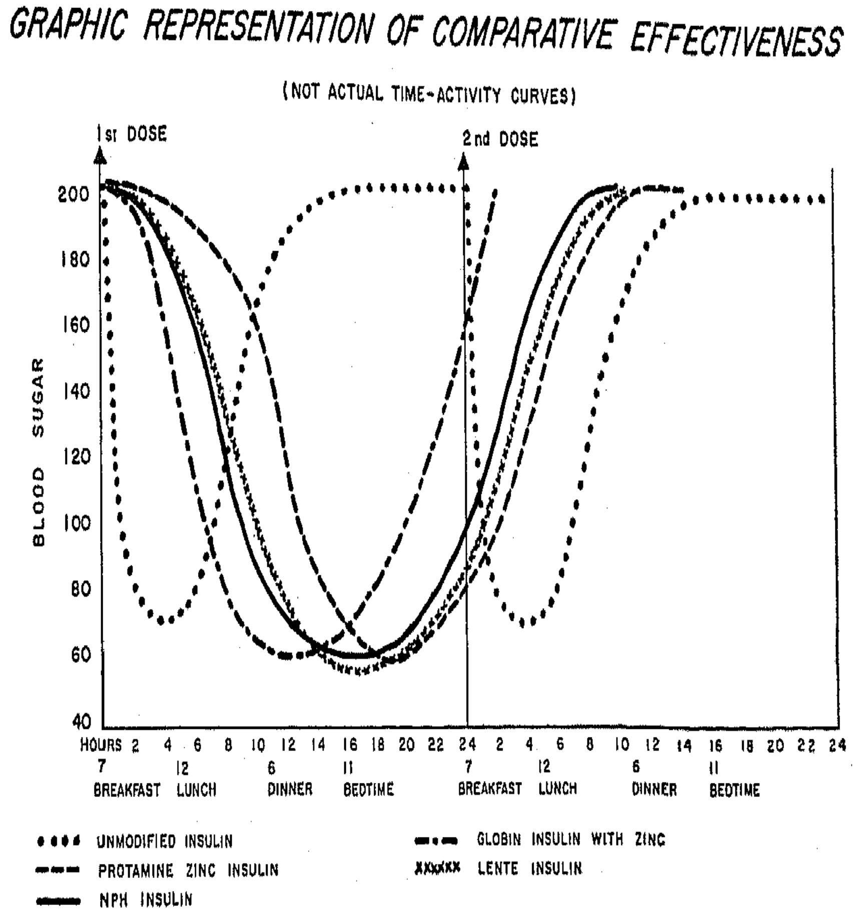


FIG. 54-5. Schematic comparison of time effects of various insulins. (From Peck, personal communication, 1956).

This product is a clear, almost colorless water solution containing 40 or 80 units in each milliliter. It is modified by the addition of 3.04 mg. of purified globin and 0.24 mg. of zinc in the form of zinc chloride to each milliliter.

The globin used is derived from the hemoglobin of beef blood. Hydrolysis of the conjugated protein, hemoglobin, liberates the simple protein, globin, which is readily separated from heme, the nonprotein color-giving portion of the hemoglobin molecule. The globin is purified and sterilized by filtration methods before it is added to the other sterile ingredients of the preparation. The final preparation is also sterilized by filtration. As an added safeguard the preparation contains 0.18 per cent cresol. The pH of the final product is about 3.7; this acidity also contributes to the maintenance of sterility and to the stability of the preparation.

Although globin zinc insulin is newer than protamine zinc insulin, wide experience with this substance has shown it to possess certain advantages, although not all clinicians are of one accord in this respect. Globin zinc insulin is a clear solution and requires no agitation before use.

Protamine zinc insulin and NPH insulin are suspensions and must be thoroughly shaken before use. Herein lies a danger of dosage variation which is theoretically objectionable in insulin therapy but has shown no practical disadvantages. The onset of the actions of globin zinc insulin and NPH insulin are more prompt than that of protamine zinc insulin. In certain patients this obviates the necessity of 2 injections in the morning, 1 of ordinary insulin and 1 of protamine zinc insulin. In other cases an evening dose of globin zinc insulin may have to be given in order to control the rising nocturnal blood sugar levels.

In a review of the literature there are many observers who hold the view that globin zinc insulin offers no advantage over protamine zinc insulin except in a small group of patients. They make exception, however, in cases which are allergic to protamine zinc insulin. On the other hand, other groups of investigators have reported an advantage from the use of globin zinc insulin. Among these Page and Bauman (1944) reported that cutaneous reactions to globin zinc insulin were less frequent than to protamine zinc insulin in allergic and nonallergic individuals.

Duncan (1952) believes that simplification of insulin therapy without sacrifice of efficiency should be urged in the treatment of patients with severe diabetes. On the basis of the demonstrated relative effects of the various insulins and the relative severity of the diabetes, he presents 3 plans of insulin therapy: (1) a single daily dose of globin insulin or of NPH insulin; (2) a single daily injection of a mixture of NPH and regular insulin; and (3) a mixture of NPH and regular insulin before breakfast and a small dose of NPH insulin before or after supper. Jackson (1953) has obtained excellent results when using 2 doses daily of globin insulin or NPH insulin in the treatment of severe juvenile diabetes.

**Isophane Insulin Injection, U.S.P., NPH Insulin.** As a result of extensive experimentation to discover a more satisfactory preparation of insulin, a crystalline form of protamine insulin designated as NPH insulin was developed in Hagedorn's laboratory. This is a type of insulin having a "time activity" best adapted to the requirements of the majority of patients. The letters NPH refer to *neutral protamine Hagedorn* insulin.

NPH insulin is a distinct entity comprising a suspension of crystals of insulin, protamine, and zinc. The crystals are prepared under special conditions discovered by Krayenbuhl and Rosenberg (1951) and represent a crystalline form of protamine zinc insulin. The active material is present in a finely-divided, insoluble, milky white crystalline precipitate. The vial of NPH insulin must be inverted several times before a dose is withdrawn, as is the case with protamine zinc insulin.

During the development of NPH insulin, more than a score of so-called intermediate-acting preparations were tested. The most generally useful of these have been the modifications which have acted in the range exhibited by 2:1 admixtures of insulin and protamine zinc insulin.

The action of NPH insulin is intermediate between the rapid but short effect of insulin and the very slow but prolonged action of protamine zinc insulin. NPH insulin appears to possess the very desirable properties of prolonged effect, sufficient to assure satisfactory maintenance of blood sugar levels during fasting at night, and a prompt onset of action, which is additive to the overlapping effect of the prior dose.

The daily use of NPH insulin generally insures adequate control of the after breakfast rise in blood sugar, which formerly required a supplemental dose of unmodified insulin. This form of insulin has a "time activity" similar to that of a 2:1 mixture of insulin and protamine zinc insulin. It possesses the additional advantage of requiring only a *single daily injection* in the majority of cases without the necessity of extemporaneous mixing. If needed, regular insulin may be added to the injection of NPH insulin and will retain most of the "quick" effect. Since NPH insulin is prepared in a highly purified stable form as crystals, its availability simplifies and improves the management of the average diabetic patient.

**Insulin Zinc Suspension, U.S.P., Lente Insulin.** The basic principle involved in the prolongation of action of insulin has been the production of a material with low solubility at the pH of the body fluids (approximately 7.4). Relative insolubility of different modifications has accounted for the various intermediate timing characteristics seen when one uses mixtures of protamine zinc insulin and unmodified insulin, NPH insulin, or globin insulin with zinc.

Prior to the advent of lente insulin, the interaction of insulin with a basic protein was employed to effect the desired degree of insolubility. A new concept of the chemistry of insulin and zinc has made possible the formation of a relatively insoluble insulin without the need for a modifying protein. Although it had been shown as early as 1935 that zinc had a delaying action on the absorption of insulin, the precise mechanism was not extensively investigated until Hallas-Møller *et al.* (1951) reported on a series of experiments which clarified this relationship.

When the concentration of zinc was increased to 10 times the amount required for the formation of soluble zinc-insulin crystals and when the buffer solution was simultaneously changed from phosphate to acetate, the higher concentration of zinc could be made to combine with the insulin in such a way that the resulting product was insoluble at pH 7.4. Two physical forms of the high-zinc insulin compound can be produced by careful adjustment of the pH, one crystalline and one amorphous. The crystalline form is much more insoluble and therefore very long-acting. The amorphous form presents more surface area to the body fluids and is more quickly absorbed. Using the basic term "lente" to indicate slow action, the 2 preparations were designated *ultra-lente* for the very long-acting crystalline form and *semi-lente* for the amorphous form of shorter action.

Clinical evaluation disclosed that perhaps the most practical timing characteristic could be achieved by utilizing a portion of each physical form in a mixture consisting of approximately 70 per cent of the *ultra-lente* form and 30 per cent of the semi-lente form. This mixture, designated

simply as *lente insulin*, has characteristics almost precisely the same as NPH insulin or the 2:1 mixture of unmodified insulin and protamine zinc insulin. These preparations are similar in clinical effectiveness, but lente insulin has the inherent advantage of being free of a foreign modifying protein.

Haunz (1955) critically studied *lente insulin* in 200 diabetics. He concluded that *lente insulin* can be substituted unit for unit for NPH insulin; however, it seemed more satisfactory to use a slightly lower dose of *lente insulin* in the beginning with this agent. The control of his patients was "smoother" and insulin reactions milder and less frequent than with other long-acting insulins. Allergic responses are minimized because of the absence of foreign protein. Haunz emphasizes that with a variety of long-acting insulins available the clinician should fit the insulin to the patient and not the patient to the insulin.

A summary of the characteristics of the commonly used insulin preparations is shown in Table 54–1.

**Other uses of insulin.** Insulin has been used with success in the treatment of malnutrition in nondiabetic individuals. It stimulates the appetite and apparently does no harm. Insulin is used to produce convulsions and coma in the treatment of schizophrenia. In treatment of the affective psychoses, it has been largely replaced by electric shock therapy. In carefully-selected cases of schizophrenia, however, and particularly in the catatonic and paranoic types, insulin coma appears to be of special value.

In the treatment of acute alcoholism the injection of insulin and glucose has been found efficacious in rapidly reducing the alcoholic content of the blood and tissue, page 288.

In patients with duodenal ulcers and in normal individuals the intravenous administration of insulin causes a stimulation of gastric secretion (Olson and Necheles, 1955). The secretion of acid and fluid drops during the first 30 minutes and then rises to its highest value at 60 minutes after the injection. Suppression of gastric secretion parallels the hypoglycemia and stimulation of secretion coincides with the rising blood sugar levels.

### ORAL HYPOGLYCEMIC AGENTS IN DIABETES

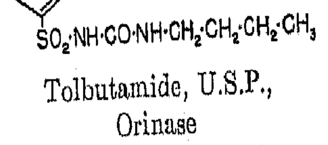
Four decades have passed since synthalin (decamethylenediguanidine) was used as a synthetic substitute for insulin in the treatment of diabetes. The compound was abandoned owing to its inadequacy as an insulin substitute and because of its hepatotoxic nature. Janbon *et al.* (1942) demonstrated that certain compounds related to the sulfonamides produced hypoglycemia when administered to rabbits and dogs. Franke and Fuchs (1955) studied the effect of 1-butyl-3-sulfanilylurea in human diabetes. They observed a lowering of the blood sugar and a disappearance of glycosuria in patients not receiving insulin. With those on an established insulin regimen the insulin dosage was diminished or in some cases discontinued. Young diabetics did not respond well to the treatment. The dosage schedule was usually 1 gm. daily. No untoward side effects were observed.

It appears now, after many laboratory and clinical investigations of various compounds related to the sulfonamides and guanidine, that there are several agents capable of producing hypoglycemia. These agents will be considered in the chronologic order of their availability as drugs used in the treatment of diabetes.

1. Carbutamide (BZ 55) 1-butyl-3-sulfanilylurea (previously mentioned)
2. Orinase (tolbutamide) (U 2043) 1-butyl-3-*p*-tolylsulfonylurea

After 3 years of extensive laboratory investigation and comprehensive clinical trial in the hands of thousands of physicians, Carbutamide was withdrawn from clinical trial by its producers. This was due to the occurrence of side effects in many patients of an allergic character often manifested by sulfonamide therapy. Principally, however, Carbutamide was discarded owing to its toxic action on the liver. Orinase, on the other hand, has not elicited hepatic toxicity and is available for the treatment of certain cases of diabetes.

**Tolbutamide U.S.P. (Orinase).** Tolbutamide was the first compound available for the treatment of diabetes other than insulin. Its structure is shown in the formula.



Tolbutamide, U.S.P.,
Orinase
1-butyl-3-*p*-tolylsulfonylurea

Tolbutamide is a white crystalline powder

## TABLE 54-1

*Summary of Insulin Preparations*

| Preparation | Insulin Injection | Semi-Lente Insulin | Globin Zinc Insulin | Isophane Insulin Suspension (NPH Insulin) | Insulin Zinc Suspension (Lente Insulin) | Protamine Zinc Insulin Suspension | Ultra-Lente Insulin |
|---|---|---|---|---|---|---|---|
| Official status | U.S.P. | U.S.P. | U.S.P. | U.S.P. | U.S.P. | U.S.P. | Unofficial |
| Description | Acid solution pH 2.5–3.5 | Neutral suspension pH 7.1–7.5 | Acid solution pH 3.4–3.8 | Neutral suspension pH 7.1–7.4 | Neutral suspension pH 7.1–7.5 | Neutral suspension pH 7.1–7.4 | Neutral suspension pH 7.1–7.5 |
| Concentration available, U./ml. | 40, 80, 100, 500, 5000 | 40, 80 | 40, 80 | 40, 80 | 40, 80 | 40, 80 | 40, 80 |
| Modifying protein amount per 100 U. | None | None | Globin 3.6–4.0 mg. | Protamine 0.3–0.6 mg. | None | Protamine 1.0–1.5 mg. | None |
| Proportion of bound insulin | None | None | 100% | 100% | None | 100% | None |
| Zinc amount per 100 U. | 0–0.04 mg. | 0.2–0.25 mg. | 0.25–0.35 mg. | 0.016–0.04 mg. | 0.2–0.25 mg. | 0.2–0.25 mg. | 0.2–0.25 mg. |
| Route of administration | Intravenous or subcutaneous | Subcutaneous only | Subcutaneous only | Subcutaneous only | Subcutaneous only | Subcutaneous only | Subcutaneous only |
| Characteristic action: | Very rapid | Rapid | Rapid | Rapid | Rapid | Slow | Slow |
| Onset | 1 hr. | 1 to 2 hrs. | 1 to 2 hrs. | 1 to 2 hrs. | 1 to 2 hrs. | 4 to 6 hrs. | 4 to 6 hrs. |
| Peak | 2 to 3 hrs. | 2 to 4 hrs. | 6 to 12 hrs. | 8 to 12 hrs. | 8 to 12 hrs. | 12 to 16 hrs. | 12 to 16 hrs. |
| Duration | 6 to 8 hrs. | 8 to 12 hrs. | 12 to 18 hrs. | 12 to 24 hrs. | 12 to 24 hrs. | 16 to 36 hrs. | 16 to 36 hrs. |

which is nearly insoluble in water. The formula of tolbutamide shows that, unlike the common sulfonamide drugs, it contains no free amino group para to the sulfonamide grouping. Tolbutamide contains a methyl group in this position which establishes a fundamental difference in structure. It is devoid of antibacterial activity. It is not acetylated in the body. Its elicits no goitrogenic action on the thyroid gland.

**Absorption, fate, and excretion.** Upon oral administration, tolbutamide is readily absorbed from the gastrointestinal tract. It is detectable in the plasma 1 hour after administration, and blood levels reach a maximum in 3 to 4 hours. Approximately 90 per cent of the tolbutamide administered is excreted in the urine within 3 days. During its sojourn in the body the methyl group is oxidized to a carboxyl group, and this totally inactive metabolite is excreted by the kidney in the urine. As much as 75 per cent of the administered tolbutamide is converted into this carboxy derivative and excreted within 24 hours. This metabolite is quite water-soluble especially with the increasing pH of the urine so that the danger of crystalluria is negligible. The presence of the metabolite in the urine will cause a positive test for albumin (pseudo-albuminuria).

**Hypoglycemic action.** The administration of 3 gm. of tolbutamide to nondiabetic, fasting individuals will cause about a 30 per cent fall in blood sugar in about 1 hour. The return to the normal glycemic level occurs within 6 to 12 hours. The oral administration of tolbutamide 50 mg./kg. elicits approximately the same degree of hypoglycemia as does 0.1 unit/kg. of insulin intravenously.

In the diabetic patient the hypoglycemia is of more gradual onset. As stated previously, in normal individuals the maximal hypoglycemia occurs within 1 hour; in diabetics, the maximal response is achieved within 5 to 8 hours. The average fall in blood sugar upon the oral ingestion of 3 gm. of tolbutamide in normal individuals is 45.9 per cent, and 46.3 per cent for tolbutamide in responsive diabetics. The optimal dose appears to be about 3 gm.; larger doses usually induce no greater degree of hypoglycemia.

**Mechanism of action of tolbutamide.** Many of the problems that arise in explaining the hypoglycemic action of tolbutamide stem from the inadequacy of our knowledge of the action of insulin. Many theories have been proposed and later rejected. Among these were the inactivation of insulinase and also the inhibition of glucose-6-phosphatase. The amount of tolbutamide required in each instance exceeds the levels required to evoke hypoglycemia, and hence each concept appears untenable.

The consensus is that tolbutamide causes insulin to be released from the beta cells of the islet tissue. It is effective in diabetes when residual insulin is available. It is ineffective when no insulin remain in the pancreas. Lazarus and Volk (1958) showed that the hypoglycemic activity of tolbutamide is proportional to the number of insulin granules demonstrable in the beta cells at the time the drug is administered.

There has been much work carried out in order to determine how the sulfonylurea drugs cause the beta cells to release insulin. One hypothesis suggests that the compounds establish weak zinc insulin complexes enabling insulin to leave the beta cells. Sund and Wallenfels (1961) showed that sulfonylurea compounds split high molecular weight insulin polymers, as they probably exist in the beta cells, forming smaller units. These smaller molecules are capable of diffusing through the cell membranes. No one concept adequately explains the effect.

Another property of the sulfonylurea drugs is also of special interest. Their hypoglycemic effect in animals is limited to their use at comparatively low dosage levels. For example, in rabbits at dosage levels of 2 gm./kg. a hyperglycemic action is observed. This has been shown to be due to the release of catecholamines from the adrenal medulla; an action similar to the insulin-releasing action from the beta cells at low dosages (Bänder, 1962).

When residual insulin is present in the pancreas there are certain advantages that appear to accrue from its release. For example, all endogenous insulin from the pancreas enters the liver via the portal vein, and much of it is retained for hepatic metabolic processes. The remainder of the hormone enters the general circulation via the hepatic vein as peripheral needs occur. Injected insulin enters the general circulation in amounts and at rates quite different from endogenous insulin. Far smaller quantities enter and leave the liver. In addition, it has been shown that the amino acid sequence in insulins from various species differs. It is possible that this difference in structure may be of significance in the control of the diabetic patient.

Tolbutamide has been shown also to suppress the depolymerization of hepatic glycogen to form glucose. This response to the drug is achieved only when "permissive" amounts of insulin are available (Foa and Galansino, 1959). This action corresponds to the effect of subcutaneous injections of insulin. Only when insulin is given intra-arterially does it evoke marked arterio-venous glucose differences indicating the utilization of glucose by skeletal muscle.

There are also indications that tolbutamide may produce beta cell regeneration and islet hyperplasia (Gepts, 1959). Fajans and Conn (1960) demonstrated a marked improvement in the glucose tolerance test of a juvenile prediabetic after 11 months of treatment with tolbutamide. It is hoped that this effect of tolbutamide will be confirmed, for it provides further rationale for the treatment of diabetes with the sulfonylurea compounds and may elucidate the etiology of the disease.

**Clinical studies with tolbutamide.** Miller and Craig (1956) used tolbutamide successfully in the management of a limited number of diabetics. Hypoglycemia was produced by tolbutamide in a partially-depancreatized patient. Diabetes associated with Cushing's syndrome responded well to tolbutamide treatment. They found no toxic symptoms in a 6 months' trial with tolbutamide.

Dolger (1956) reported his findings with tolbutamide therapy in 700 patients. He succinctly states, "Orinase's success in juvenile diabetes is so rare that it can be considered zero. But in the age group between 20 and 40 years, it will be successful in 1 out of 3 patients; and in the age group from 40 years on it will be successful in 4 out of 5 patients." The great majority of diabetics fall within this last mentioned age group and therefore have an 80 per cent chance of success with oral tolbutamide therapy.

In Joslin's clinic, Krall *et al.* (1958) reported on the treatment of over 1400 diabetic patients. Although the effectiveness for tolbutamide is claimed to be of the order of 60 to 70 per cent, Krall *et al.* take a more conservative view. They state, "A more realistic over-all percentage of effectiveness might be 20 to 25 per cent. Untoward side effects were encountered in less than one per cent of these patients. It is estimated that more than ½ million of the diabetic population of the United States have received tolbutamide therapy at least for a period of time. This is a large segment of the estimated diabetic population of 2 million."

More extensive evaluation of the effectiveness of tolbutamide in diabetes indicates that success in treatment may be expected in about ⅔ of the patients in the age group 40 to 60 years and a slightly higher proportion in those over 60 years.

**Side effects of tolbutamide.** As with insulin, but to a lesser degree, one side effect of tolbutamide is hypoglycemia. This usually occurs in the transition period between insulin and tolbutamide therapy. Other untoward side effects are not serious or persistent; these consist of *gastrointestinal disturbance, headache, allergic skin manifestations* and *alcoholic intolerance.* Usually these side effects can be mitigated by dosage reduction.

Schnall and Wiener (1958) reported a case of nephrosis occurring during therapy with tolbutamide. Ellenberg (1959) reported 3 cases of diabetic neuropathy following the institution of control of hyperglycemia with tolbutamide. This was not considered a toxic effect of the drug but a manifestation of the disease. Severe cases of protracted and probably lethal aplastic anemia while taking tolbutamide have been reported (Yost, 1959; Brod, 1959).

Bloodworth and Hamwi (1961) reported their pathologic findings in 20 autopsied patients who had received tolbutamide therapy for periods of 30 days to 2 years. They state "Most patients showed microgranulomata composed of 20 to 50 cells, predominantly histiocytes, lymphocytes, plasma cells, and occasional eosinophilic polymorphonuclear leukocytes. These lesions appeared to occupy defects in the tissue and occasionally contained eosinophilic debris suggestive of connective tissue fibrinoid changes. Similar microgranulomata are not uncommon, but the incidence was higher apparently than in diabetics treated with insulin. Myocarditis was present in 11 of 17 cases studied, and may have contributed to the cause of death in 1 patient. These changes are similar to but less severe than those produced by sulfonamide hypersensitivity."

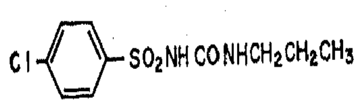
Hamwi and Serbin (1959) reviewed a series of over 9000 diabetics treated with tolbutamide. The incidence of all side effects was 3.1 per cent; of these, gastrointestinal disturbance was 1.4 per cent, skin disorders 1.1 per cent, hematologic disorders 0.2 per cent, and all others 0.4 per cent. Because of the side effects treatment was stopped in only 1.53 per cent. It does appear that the drug is well tolerated by a very large segment of diabetics.

The dosage of tolbutamide for a suitable patient not receiving insulin is instituted as follows: first day, 3 gm. (6 tablets), second day, 2 gm.; and the third day, 1 gm. Thereafter, the daily dose for maintenance will vary from 0.5 to 1.5 gm. (1 to 3 tablets). The medication may be taken as a single dose in the morning or spaced throughout the day.

Patients whose insulin requirements are less than 40 units daily may be given tolbutamide with a 30 to 50 per cent reduction in insulin dosage. Further reduction in insulin dosage is instituted as the tolbutamide response becomes effective.

Diabetic treatment is a long-term investment in therapy, and it will take much time to assess the ultimate value of tolbutamide in the routine treatment of middle-aged and older diabetics. Yet its discovery and the success clinically of tolbutamide have fanned the fires of enthusiasm for newer agents in the treatment of diabetes. Chlorpropamide, another sulfonylurea drug, is available for the treatment of diabetes, and a reawakening of the interest in the guanidine derivatives, such as synthalin, has resulted in the availability of phenformin, a diguanide, in the treatment of the disease. Furthermore, implicit in the statement of the renewed interest in the intriguing problem of carbohydrate metabolism, is the fact that many heretofore obscure facets of the problem have been elucidated by the intense effort being exerted in the field.

**Chlorpropamide.** Chlorpropamide is an oral hypoglycemic agent closely related structurally to tolbutamide as shown in the formula.



Chlorpropamide-Diabinese
1-(*p*-chlorobenzenesulfonyl)-3-propylurea

Chlorpropamide occurs as a white, crystalline powder which is sparingly soluble in water. Its solubility in water is enhanced by the presence of alkalies.

**Pharmacologic response to chlorpropamide.** The principal pharmacologic response to chlorpropamide is *hypoglycemia.* Jaeger *et al.* (1959) studied the action of chlorpropamide on the various physiologic systems. Chlorpropamide failed to produce specific blood pressure, respiratory or diuretic responses in doses which evoked profound hypoglycemia. Very high dosage levels of chlorpropamide in various laboratory animals elicited general weakness, ataxia, and incoordination. Chronic feeding studies in animals produced no injury to the elements of blood or principal viscera.

**Absorption, fate and excretion.** The fate of chlorpropamide in man was studied by Johnson *et al.* (1959) using chlorpropamide labeled with $S^{35}$. Chlorpropamide is readily absorbed from the gastrointestinal tract; while circulating in the blood it is bound partially by serum proteins. Chlorpropamide is excreted by the kidneys in the urine. The initial disappearance from the blood for the major portion of the dose has a half-life period of 32 hours and the half-life period for the remainder is 16 days. Metabolic alteration of the compound occurs to a limited degree. The primary product of excretion in man is unaltered chlorpropamide. A small fraction of the ingested drug may be converted into *p*-chlorobenzenesulfonamide. There appear to be 2 important differences between the metabolic fate of chlorpropamide and that of tolbutamide: (1) tolbutamide is oxidized to a carboxylic acid and excreted quite rapidly; (2) chlorpropamide is excreted mainly unchanged and enjoys a longer sojourn in the body.

**Mechanism of action of chlorpropamide.** It appears from the evidence available that the hypoglycemic action of chlorpropamide is identical with that of tolbutamide, page 867. It is, however, longer acting and may be effectively administered in smaller doses.

**Clinical use of chlorpropamide.** The clinical use of chlorpropamide is identical with that discussed under tolbutamide. The daily maintenance dose of chlorpropamide is 250 to 500 mg.; however, doses of 750 to 1000 mg. are often given. There are numerous clinical studies reported on the use of chlorpropamide in diabetes. The consensus appears to indicate that chlorpropamide is a more powerful hypoglycemic agent than tolbutamide, and hypoglycemic reactions are more frequently encountered. Furthermore, there have been encountered a greater frequency of untoward side reactions when the maintenance dose is exceeded. The clinical evaluation of Canessa *et al.* (1959) is cited as a typical response to chlorpropamide therapy. The drug was given to 80 diabetics in a dosage range of 125 to 1000 mg. daily. Results of treatment were good in 55 per cent, fair in 29 per cent, and poor in 16 per cent. The plasma levels of chlorpropamide were between 5 and 10 mg. per cent.

There are those who contend that chlorpropamide treatment is successful in a greater percentage of the cases treated than is tolbutamide. Thus, Fineberg (1960) found chlorpropamide therapy satisfactory in 76 per cent and tolbutamide in 43 per cent of the cases treated. Although the number was small, they were carefully controlled. Fineberg's degree of success with tolbutamide appears to be below the general average of about 66 per cent. It is established that certain diabetics are better controlled with chlorpropamide and others are better treated with tolbutamide. It is a matter of tailor-fitting the sulfonylurea compound to the patient's needs.

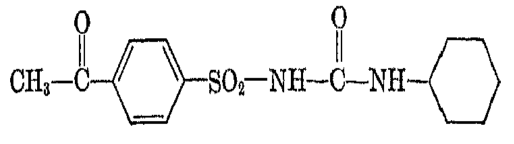
**Side effects of chlorpropamide.** Hamwi *et al.* (1959) in a study of 5000 patients receiving chlorpropamide therapy recorded an incidence of 8.5 per cent side effects compared with about 3 per cent with tolbutamide. The side effects of chlorpropamide consist of *jaundice*, *nausea*, *substernal pain*, *pruritis*, *fatigue*, *anorexia*, and *agranulocytosis*. As previously mentioned, hypoglycemia may be more frequently encountered with chlorpropamide than with tolbutamide because of the more powerful action of the former drug.

As with tolbutamide therapy, intolerance to alcohol is also encountered. Rothfeld *et al.* (1960) encountered a case of ulcerative proctocolitis resulting from chlorpropamide therapy. Obstructive jaundice and skin lesions also accompanied the lesions of the intestinal tract.

The availability of chlorpropamide makes it possible to extend the scope of oral diabetic therapy. In general, however, the 2 drugs have a common mechanism of action; comparable degrees of success are achieved by each, and each has its limitations owing to the lack of effectiveness in juvenile diabetics and younger persons in whom the disease is not stabilized.

**Acetohexamide (Dymelor).** Another oral hypoglycemic agent of the sulfonylurea series is the newer drug acetohexamide. Its structure is shown in the formula.

**Mechanism of action of acetohexamide.** The hypoglycemic action of this compound stems from the same activity exhibited by the previously described sulfonylurea derivatives. It stimulates the release of endogenous insulin. There also appears to be some inhibition of the depolymerization of hepatic glycogen into glucose. An interesting facet of the action of acetohexamide is its prolonged duration of hypoglycemia. This appears to be due to the fact that the *p*-acetyl group is reduced by the tissues and the reduction product evokes the same response as does the parent molecule. Approximately 60 per cent of the compound is excreted by kidney in the urine in this reduced form.

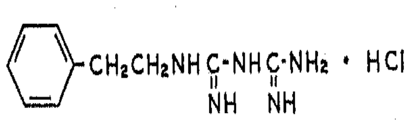


Acetohexamide
Dymelor
N-(*p*-acetylphenylsulfonyl)-N′-cyclohexylurea

**Clinical use of acetohexamide.** Like the other sulfonylurea derivatives, acetohexamide is recommended in the treatment of selected patients with stable diabetes mellitus. It is not valuable in juvenile diabetes. The prolonged hypoglycemic effect of the compound makes it possible to control most patients with 500 mg. (1 tablet) or less daily. The dose may be increased, if necessary, to 1500 mg. daily. If satisfactory control is not achieved with this dosage level, the patient is not likely to be successfully treated with the drug.

The side effects of the drug appear to be few in a survey of 1,500 cases of diabetes treated with acetohexamide. *Gastrointestinal distress* and *skin rash* have been encountered. *Headache* and *nervousness* have also been observed. Four cases of *jaundice* have been reported in 40,000 cases treated with the drug. The jaundice was reversible and disappeared upon the discontinuance of the drug. Acetohexamide is a welcome addition to antidiabetic therapy, which extends the choice of the physician to a third and dependable sulfonylurea derivative.

**Phenformin Hydrochloride (DBI).** Phenformin is $N^1$-betaphenethylbiguanide hydrochloride, as shown in the formula.



$$\text{-CH}_2\text{CH}_2\text{NH}\underset{\underset{\text{NH}}{\|}}{\text{C}}\text{-NH}\underset{\underset{\text{NH}}{\|}}{\text{C}}\text{-NH}_2 \cdot \text{HCl}$$

Phenformin
(DBI) (PEDG)
phenylethylbiguanide

Phenformin occurs as a white, crystalline powder soluble in water and alcohol.

**Pharmacologic response to phenformin.** The principal pharmacologic response to phenformin is *hypoglycemia*. From the evidence available, it appears that phenformin evokes no marked pharmacologic response other than hypoglycemia. At high dosage levels the compound elicits a slight depressant action on the spontaneous motor activity of rats and a mild antidiuretic effect. Upon intravenous injection into dogs phenformin produces a transient rise in blood pressure and an adrenergic block. Administered by any other route it does not potentiate or block the actions of epinephrine, acetylcholine or histamine on the circulation (Ungar *et al.*, 1957).

**Mechanism of action of phenformin.** From the numerous studies conducted on the mechanism of the hypoglycemic action of phenformin, it is apparent that its action differs from that of the sulfonylureas. Williams and Steiner (1959) produced evidence to show that the action of phenformin does not enhance the action of insulin, increase its production, or retard its degradation. It is not an inhibitor of glucagon. Phenformin does not enhance the oxidation of glucose or increase the respiratory quotient. Phenformin decreases the glucose output of the liver and increases the glucose uptake of muscle. Unlike insulin, however, it does not increase muscle glycogen, but evokes an increase in lactic acid. For example, in liver slices phenformin elicits a decrease in glycogen but not an increase in glucose. Instead, the lactic acid level is enhanced. Irreversible lactic acidosis has been associated with phenformin therapy (Tranquada *et al.*, 1963).

Wick *et al.* (1958) showed that in adipose tissue phenformin decreased glucose oxidation and the conversion of glucose to glycogen and also total lipid. These experiments indicate that phenformin inhibits glucose oxidative metabolism and promotes anaerobic glycolysis. Steiner and Williams (1958) suggest that phenformin inhibits either cytochrome oxidase or succinic dehydrogenase. The concentrations required to produce this effect, however, are far greater than those corresponding to therapeutic doses. The *in vitro* activity on enzymes appears to be nonspecific, and it is doubtful if it can be correlated with hypoglycemic activity (Ungar *et al.*, 1960).

Phenformin is retained in the gastric juice prior to absorption. After absorption it accumulates in the liver. About 95 per cent of the dose is excreted in the urine within 24 hours.

**Clinical use of phenformin.** Like the sulfonylureas, phenformin is used in diabetes as a hypoglycemic agent. Clinical studies with phenformin in diabetes carried out by various investigators have demonstrated that the compound is capable of producing hypoglycemia in various types of diabetes (Krall *et al.*, 1958; Lambert, 1959; Pomeranze *et al.*, 1957). Evidence of toxicity appears to be lacking in some clinical trials, some of them extending over 2 to 3 years.

Krall and Bradley (1959) in the Joslin clinic used phenformin in 173 cases and achieved hypoglycemia in 88 per cent. On the other hand, 38 per cent could not tolerate the drug even though it was effective in 26 per cent. The principal untoward side effects encountered which necessitated the discontinuance of the drug were *anorexia*, *nausea*, *vomiting*, and *diarrhea*. Often the side effects subsided when the dosage level was reduced. The remarkable feature of the action of phenformin is that of the patients studied in this group 30 per cent had diabetes of juvenile onset. Krall *et al.* state, "The most important contribution of phenformin may be in the treatment of the unstable and severe 'reaction-prone' diabetics. Some of these may be stabilized by a combination of phenformin, when tolerated, and smaller injections of insulin." Krall (1959) states, "Phenformin shows the unique ability to cooperate with insulin, and in a number of patients this drug has provided better regulation with fewer severe reactions and a subsequent more normal life." Krall has found no evidence of kidney or liver damage or blood dyscrasias in several thousand patients treated with phenformin for almost 3 years. The usual dosage schedule of phenformin is 25 to 100 mg. or more per day in divided doses, depending on the hypoglycemic response.

**Side effects of phenformin.** Skillman *et al.* (1959) reviewed the cases of 2000 patients treated with phenformin. Side effects were encountered in 32 per cent, all of these were gastrointestinal distress. As previously mentioned acidosis from excessive lactic acid formation may occur especially if renal function is impaired.

Other biguanides are also hypoglycemic agents, for example *n*-amyl (DBB) and *n*-butyl (DBV). These agents act in the same manner as do phenformin and differ only in the quantitative response to their action. Phenformin appears to be the preferred compound.

In the treatment of diabetes, it is clear that the sulfonylureas and phenformin have supplemented insulin. With a carefully regulated diet and the addition of the oral hypoglycemic agents supplementing insulin, the problem of treating most diabetics can be handled adequately. The disease is individualistic and the proper treatment of each case is a challenge to explore the facets of the distorted carbohydrate metabolic pattern. Krall (1959) very cogently states, "There is no royal road to diabetes regulation and treatment and no shibboleth that is an easy password to successful therapy".

### DIABETIC FOODS AND SUGAR SUBSTITUTES

For many years one of the approaches to the treatment of diabetes, especially in the pre-insulin days, was the discovery of a sugar or similar substance which would metabolize in the body without insulin. The number of such substances studied is large. Not any has been found to be successful. But many diabetic foods are still employed.

Jerusalem artichokes, Burdock root, washed bran, caromel, casein, levulose, dihydroxyacetone, and other substances have been suggested. Today a substance which is still used is sorbitol, page 297. This substance was used for years by the German clinicians before it was employed in this country. This sugar alcohol was found to be nontoxic in laboratory animals and man by Ellis and Krantz (1941). These investigators used sorbitol in the diets of 13 moderately severe diabetics. Although sorbitol raised the respiratory quotient of normal persons and mild diabetics, it was incapable of doing this in moderately severe diabetics. It did not, however, produce hyperglycemia. In the liver sorbitol is oxidized to levulose and polymerized into glycogen. Therefore, when glycogenolysis occurs providing for glucose utilization in the periphery, insulin is required for its catabolism.

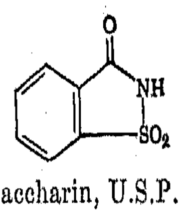
Steinke *et al.* (1961) supplemented the diets of 143 children in a diabetic camp with 40 gm. of sorbitol daily in 3 portions. It was well tolerated without gastrointestinal symptoms or the necessity of increasing the insulin dosage. Blood sugar levels were not elevated. Ketone bodies and free fatty acid values were not significantly affected by the ingestion of sorbitol. It is interesting to observe that concern is again awakening in this compound with respect to its use in diabetes.

**Sugar and the American diet.** In the year 1800 sugar was about $6.00 a pound and very sparingly available. In 1964 sugar was about 20 cents a pound, and the consumption of the carbohydrate by the people in the United States had risen to nearly 100 pounds per person per year. As the population of the world increases the necessity for the ingestion of more sugar will become greater since the need for the production of more calories per acre will increase. The average American eats 3000 calories of food per day or about a million calories per year. To produce a million calories of staple items of diet the following acreage is required.

| | *acre* |
|---|---|
| Sucrose (cane or beet) | 0.15 |
| Potato | 0.44 |
| Corn | 0.9 |
| Wheat | 0.9 |
| Eggs | 9.3 |
| Beef | 17 |

Sugar contains no vitamins or minerals. It is nearly 100 per cent pure as ingested and provides the sweet taste necessary to bring out the flavor of many substances such as chocolate and fruit juices. Thus, sugar enables one to ingest vitamins and minerals which would otherwise be rejected as items of diet. One hesitates to conjecture what influence the tremendous consumption of sugar will have upon the incidence of diabetes in the future. Perhaps none; possibly the islet tissue will rapidly rise in insulin production to meet its extra burdens. At least this is a fond hope.

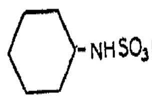
**Sweetening agents in diabetes.** Sorbitol, which was previously discussed, is an excellent sweetening agent, but it also provides calories. Saccharin, which was accidently discovered in the laboratories of Ira Remsen at the Johns Hopkins University at the turn of the century, is an intensely sweet substance. Saccharin is about 500 times sweeter than sugar. It provides no calories. The sodium salt of saccharin is called "soluble saccharin." Its structure is shown in the accompanying formula.



Saccharin, U.S.P.

*Saccharin sodium* dissolves in about 1.5 parts of water. It is readily absorbed from the gastrointestinal tract and eliminated unchanged through the kidney in the urine. In quantities in which it is used for sweetening, saccharin has been shown repeatedly to be harmless. When used in excessive amounts it sometimes provokes dyspepsia. The greatest objection that many people raise to the repetitious use of saccharin is the bitter metallic after-taste that it leaves in the mouth. Indeed, to some persons the taste is distinctly bitter and not sweet.

**Sodium Cyclamate (Sucaryl).** Sucaryl is another sweetening agent used for the purpose of providing a sweet taste for food in sugar-restricted diets. The structure of Sucaryl is shown in the accompanying formula.



Sucaryl (Cyclamate Sodium N.F.)
Sodium cyclohexylsulfamate

This synthetic sweetening agent has no caloric value. One 0.12-gm. tablet is equivalent in sweetening power to about 1 teaspoonful of sugar. In moderate amounts the compound is said to elicit no bitter after-taste. Its chemical stability permits its use in cooking and baking foods, since it is not decomposed by the heat necessary for their preparation or by boiling in solution. Cyclamate is also available as the calcium salt.

Cyclamate in food and beverages is nonhazardous, according to a report prepared by the Food Protection Committee of the National Research Council (1955).

"There is no evidence that use of the non-nutritive sweeteners, saccharin and cyclamate, for special dietary purposes is hazardous. In the case of cyclamate, unrestricted use in foods and beverages may result in the formation of soft stools, but probably without interference with other functions of the intestine and without hazard to health."

The use of artificial sweetening agents in special dietary low caloric foods supplies a comparatively small intake of these compounds. The recent rise in the use of these sweetening agents in soft drinks presents a more difficult problem, since children, pregnant and lactating women are ingesting comparatively larger quantities of these substances at more frequent intervals. The data available, especially with regard to cyclamate, do not assure that comparatively large amounts can be consumed by all persons over long periods with impunity.

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# 55

# Iodine Metabolism. Thyroid Powder and Antithyroid Agents

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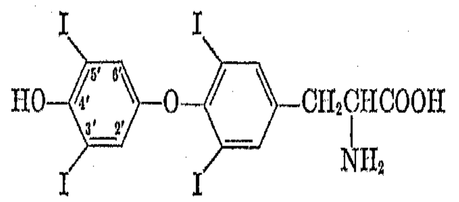
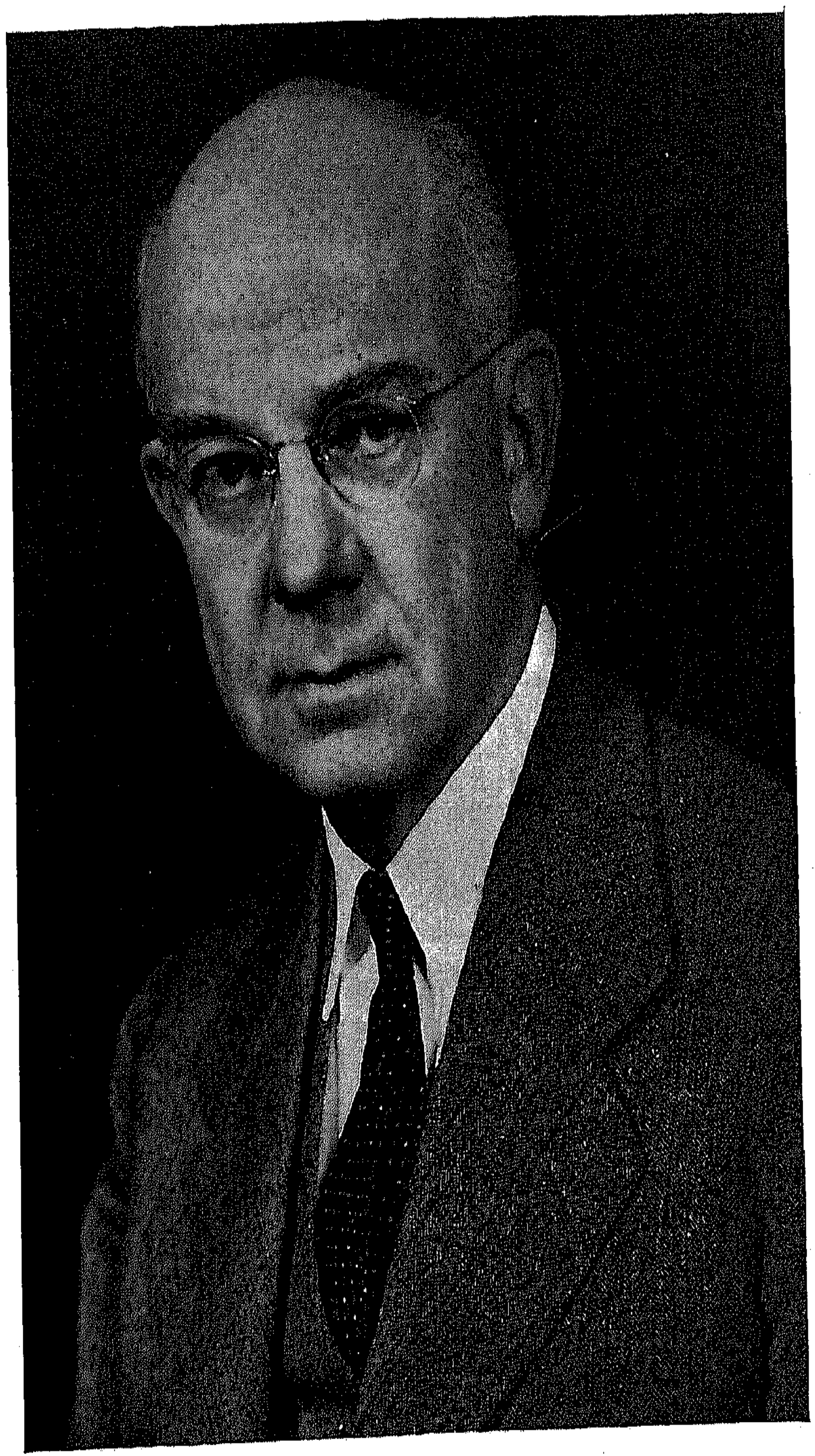
The element iodine was discovered by the French apothecary Courtois in 1811. Baumann (1895) discovered the presence of iodine in the thyroid glands of animals. Prior to this latter event Murray (1891) used a glycerin extract of the thyroid glands of animals to treat a case of myxedema. It was later observed that the activity of the gland in the treatment of cases of hypothyroidism was a function of its iodine content. The explanation of this observation became apparent on Christmas Day, 1914, when Kendall isolated crystalline thyroxin from the thyroid glands and showed that the molecule contains iodine.

In 1927 Harington and Barger demonstrated that the original structure assigned to thyroxin by Kendall was incorrect. They then synthesized thyroxin and showed it to have the following structure:



Thyroxin

Like epinephrine, naturally-occurring thyroxin is the levorotatory variety, and the levo variety is more potent than the racemic mixture. Reineke and Turner (1945) showed that the *l*-thyroxin is about twice as active as the synthetic racemic hormone. The dextro isomer of thyroxin exhibits little activity.



E. C. KENDALL

*The American biochemist who first isolated thyroxin*

"Thyroxin is utilized by the living organism to sustain a driving force for the production of energy and all types of cellular activity."

Thyroxin and triiodothyronine are the 2 hormones of the thyroid gland. Thyroxin is the hormone most readily identified and the most abundant both in the gland and in the serum. Triiodothyronine can also be found in minute quantities. No other analog of thyroxin or triiodothyronine has been found to have a metabolic potency approaching that of these 2 naturally-occurring hormones. Experiments with methyl substitutions on the outer, phenolic ring of 3,5 diiodothyronine suggest that 3′-occupancy is favorable to hormonal activity and substitution on 5′ is not (Barker, 1962). Thyroxin affects the metabolism of all tissues. The formula shows that the molecule contains 4 atoms of iodine. It therefore becomes apparent that the iodine balance of the living organism involves important endocrinologic components.

## Iodine Content of the Tissues

The thyroid gland is the depot for iodine reserves in the body. However, as early as 1902 Justus concluded that every cell in the body contains iodine. In recent years qualitative evidence has been produced which points to the correctness of this early view. The entire content of iodine in the human body is between 20 and 50 mg. This quantity is equivalent to the amount of iodine present in 0.7 ml. of Lugol's solution. Of this quantity of iodine the *muscles* contain approximately $\frac{1}{2}$, the *skin* $\frac{1}{10}$, and the *skeleton*, $\frac{1}{17}$. The blood of normal, fasting individuals contains about *10 μg. per cent of iodine.* The normal human thyroid gland contains about $\frac{1}{5}$ of the total iodine cf the body, although its mass is approximately $\frac{1}{500}$ of the body weight. The thyroid gland contains about 40,000 μg. per cent of iodine, or 0.04 per cent.

The iodine present in the body is in the form of either inorganic iodide or organically-bound iodine which may be in the form of (1) thyroxin, which is insoluble in diluted aqueous acid solutions; and (2) diiodotyrosine, which is quite soluble in dilute aqueous acid solutions. Gross and Leblond (1951), using chromatographic methods, identified other congeners of thyroxin in blood. These are monoiodotyrosine and triiodothyronine. This latter substance was shown by Gross and Pitt-Rivers (1952) to exhibit 3 to 4 times the activity of thyroxin when assayed on thiouracil-treated rats (see page 887).

## Iodine and Endemic Goiter

Goiter as a clinical entity was recognized and treated with burnt sponge and seaweed as early as the twelfth to fourteenth centuries. These are crude natural sources of iodine. William Prout (1816) was the first to use potassium iodide in the treatment of simple goiter. A. C. Maffoni (1846) made the suggestion, based upon the successful results of iodide therapy in goiter, that a deficiency of the element in drinking water was the cause of goiter. In the absence of a sufficient quantity of available iodine in the diet, the thyroid gland is thwarted in its capacity to produce adequate supplies of thyroxin. In a euthyroid individual the iodine intake is about 150 μg. daily. If by a change in diet, *i.e.*, to one deficient in iodine, the intake of the element is reduced to 15 μg. daily, the concentration of iodine in the iodide compartments of the body diminishes. The renal excretion of iodine continues, and the thyroid gland responds to its obligatory task of thyroxin synthesis with insufficient iodide supplies by excessive proliferation of the thyroid epithelium. This compensatory mechanism provides an increased blood supply to the gland from which iodine may be removed, despite the fact that the blood-iodine content has decreased. Iodine equilibrium is usually established with a daily iodine intake of 50 to 75 μg. Persons in goitrous regions frequently ingest and excrete more than 75 μg. daily even when all seafood is excluded from the diet (Greenwald, 1955). Roche *et al.* (1956) studied the iodine metabolism in a region of endemic goiter in Venezuela. They observed that individuals in this area, who suffered from a state of iodine deficiency, exhibited compensatory thyroid avidity for iodine. There was, however, no compensatory renal conservation of iodine.

This state of thyroid hyperplasia is the beginning of "endemic goiter." If iodine is supplied in the diet, the acini of the gland become filled with colloid substance, and the hyperplasia ceases. This resting stage of thyroid enlargement is referred to as a "colloid goiter." Prophylaxis against endemic goiter is now established by the presence of small quantities of iodine in table salt. In the United States 100 mg. of sodium iodide per kg. of table salt is the acceptable quantity (Kimball, 1937 *et seq.*). It is estimated that as little as 0.05 mg. of iodine daily provides sufficient halogen for human metabolic needs.

Although investigators have found dogs with endemic goiter, this condition was not produced in laboratory animals experimentally until the recent work of Follis (1959), who produced the classic lesion in hamsters.

It is now recognized that hypothyroid states can occur when individuals are enjoying a diet containing adequate iodine. Astwood *et al.* (1949) showed that certain foods contained thyroid-inhibiting constituents. An active goitrogenic agent, namely, 1,5-vinyl-2-thioöxazolidone, was isolated from various *brassicaceous* plants (cabbage family). This naturally-occurring goitrogenic agent resembles the synthetic antithyroid drugs of the *thiouracil* series (see page 887) from the standpoint of chemical constitution and pharmacologic response. The thioöxazolidone was found to be present in all of the *Brassica* seeds tested. It is present also in the edible portions of rutabaga and turnip but fortunately not in cabbage leaves. Dietary history which clearly points to the incrimination of goitrogenic foods as an important factor in goiter production is rare.

## Thyroid Requirements, Thyroxin, and Triiodothyronine

It has been estimated that the normal thyroid gland secretes approximately 200 μg. of thyroxin daily. This is synthesized in the gland from the iodide in the circulating blood. The apparent functions of the thyroid gland are: (1) to conserve iodine so that reserve stores will be available for periods of iodine deprivation, (2) to synthesize thyroxin and triiodothyronine and to secrete them for body metabolism, and (3) to expedite the degradation of excesses of thyroxin. Hormonal synthesis proceeds with great rapidity. When administered to animals, radioactive iodine ($I^{131}$) soon appears as diiodotyrosine in the thyroid gland. Following the iodination of tyrosine this product diminishes, and the iodine appears as thyroxin. Thyroxin may be deiodinated with respect to one atom of iodine to form triiodothyronine. Triiodothyronine is also synthesized by the thyroid gland by effecting a union of 1 molecule of diiodotyrosine and 1 molecule of monoiodotyrosine.

The thyroid gland is compossed of follicles, in each of which there is a layer of epithelial cells surrounding a lumen. The colloid material, consisting mainly of a mucoprotein, thyroglobin, is contained in the lumen. Within the matrix of the thyroglobin molecule the synthesis of thyroxin and triiodothyronine occurs. Although the hormonal synthesis takes place in the colloid of the follicles, the rate of production is determined by the number of follicular cells. It is these cells which synthesize and secrete thyroglobin into the colloid in order to incorporate iodine into the thyroglobin present in the colloid, and effect the decomposition of the thyroglobin, which causes the release of the hormones (Nadler, 1962).

The thyroxin and triiodothyronine transported in the plasma are mainly bound to plasma proteins. The binding is not a peptide bond linkage, as is present in thyroglobin, the storage form in the thyroid gland. As much as 95 per cent of the bound hormone is thyroxin and the remainder is triiodothyronine. Very small amounts of mono and diiodo derivatives have also been identified. The transport proteins are *thyroxin-binding globulin*, *thyroxin-binding prealbumin* and *albumin*. The binding capacities are subject to variation in pathologic conditions. In addition, the presence of free or unbound thyroxin appears to be established. The free thyroxin level is affected by alterations in the carrier binding and in turn can influence distribution, excretion, degradation, and activity of the hormone.

It has been demonstrated by various investigators that the activity of triiodothyronine is about 5 times that of thyroxin. In addition, the latent period after administration of thyroxin is longer than that which follows the administration of triiodothyronine. As mentioned previously, triiodothyronine is synthesized by the thyroid gland from monoiodo- and diodotyrosine.

The primary actions of thyroxin and triiodothyronine are to increase the metabolic rate; there is some evidence that their complete pharmacologic spectra of activity might vary. For example, thyroxin evoked a contraction of the melanophores in the skin of the South African toad *Xenopus laevis* through a neurohumoral action of a cholinergic nature, involving the release of the melanophore-stimulating hormone from the pars intermedia. Triiodothyronine failed to affect color changes in the toad's skin at a dosage level 10 times greater than the effective dose of thyroxin.

## Use of Thyroid in Hypothyroid States

In the foregoing paragraphs the endocrinologic importance of iodine was emphasized. In conditions of thyroid insufficiency the whole thyroid gland of sheep or other animals, containing iodine in the form of the thyroid hormones or their precursors, has been used most successfully.

**Thyroid, U.S.P.** Thyroid is a yellowish to buff-colored, amorphous powder. It has a slight, characteristic, meat-like odor and a salty taste. It is the cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man. The thyroid powder of the United States Pharmacopeia is assayed and standardized upon its iodine (in thyroid combination) content. It must be free from iodide and added organic iodine compounds and contain not less than 0.17 or more than 0.23 per cent of iodine in thyroid combination. This is a measure of its potential thyroid hormone content and hence of its calorigenic value. In addition to the chemical assay, many pharmaceutical producers also assay thyroid powder by its capacity to enhance the

TABLE 55-1

*Types of Peripheral Actions of Thyroid Hormones*

*1. Calorigenesis and thermoregulation*

Metabolic maintenance of most mammalian tissues, except for brain, gonads and accessory reproductive structures, spleen, lymph nodes, smooth muscle

*2. Specific aspects of intermediary metabolism*

Lipids—decreased hepatic and blood plasma cholesterol

Carbohydrate—increased utilization, mobilization of glycogen stores

Protein—increased gluconeogenesis, accelerated mobilization

Specific nutrients—increased requirement for vitamins, minerals

*3. Reproduction*

Maintenance of fertility in ovulating mammalian forms

Maintenance of uterine contents during pregnancy

Lactation

*4. Growth and development*

Metamorphosis in lower vertebrates

Broad aspects of development in young mammals —CNS, bones, teeth

Broad aspects of growth—plus growth hormone

*5. Cardiovascular system and blood*

Heart tissue metabolism especially sensitive to $T_3$, $T_4$*

C-V system—responses of heart as organ
—circulatory effects of $T_4$ marked, perhaps through sensitization to epinephrine and norepinephrine

Hematopoiesis—perhaps specific—at least tissue maintenance

*6. Water and electrolyte handling*

Specific renal effects?

*7. Nervous system*

Central—mental acuity, electrophysiological activity

Peripheral—neuromuscular functioning

---

* $T_4$ is thyroxin and $T_3$ is triiodothyronine. Certain of these altered functions of clinical importance are discussed in the following paragraphs.

oxygen consumption of athyreotic rabbits. This method enables the establishment of definite calorigenic activity in different samples of thyroid powder.

When stored under the proper conditions, thyroid powder does not lose iodine or its calorigenic potency over many years.

**Pharmacologic responses to thyroid.** Thyroid is readily absorbed from the gastrointestinal tract and hence is active when administered orally. The primary effect of the administration of thyroid is an *increase in metabolic rate.* In a thyroidectomized dog the basal metabolic rate drops to 60 per cent of its normal value. It appears therefore, that the effect of the thyroid hormones on living tissues is responsible for about 40 per cent of the oxygen uptake. It is clear that the increased metabolic rate induced by the thyroid hormones would produce multifaceted changes in the various organ systems of the body. These are summarized in table 55-1 by Barker (1962).

The site of the action of the thyroid hormones in accelerating the metabolic rate appears to be *peripheral.* The oxygen uptake of tissues of animals treated with thyroid or thyroxin is high after excision from the body. It appears that the action at an enzyme level is similar to that of dinitrophenol, *i.e.*, it prevents the utilization of energy for synthetic purposes by uncoupling phosphorylation from oxidation. On the other hand, there are those who believe that thyroxin can form a free radical and in this capacity serve as an oxidation-reduction agent protecting a vital and as yet uncharacterized enzyme system.

Sokoloff and Kaufman (1959) made an interesting contribution to our knowledge of thyroxin activity at a cellular level. They observed that thyroxin enhanced the uptake of *d,l*-leucine-1-$C^{14}$ by rat liver homogenates. At concentrations of $10^{-5}$ M thyroxin increased the amino acid conversion into protein *in vitro* and *in vivo.* The increased rate of amino acid incorporation into protein *in vivo* (thyroxin-pretreated rats) was found to be a function of the mitochondrial fraction of the liver homogenates. They suggest that the accelerated oxygen uptake evoked by thyroxin may be sequential to the enhancement of energy-requiring reactions such as protein synthesis.

It has been shown that thyroxin increased the incorporation of radioactive amino acids in the rat into the protein of liver, kidney, and heart, but not of the spleen, testis, or brain. The protein synthesis pattern followed that of stimulation of oxidative metabolism. Thus it appears that the enhancing of protein synthesis is a physiologic function of the hormone.

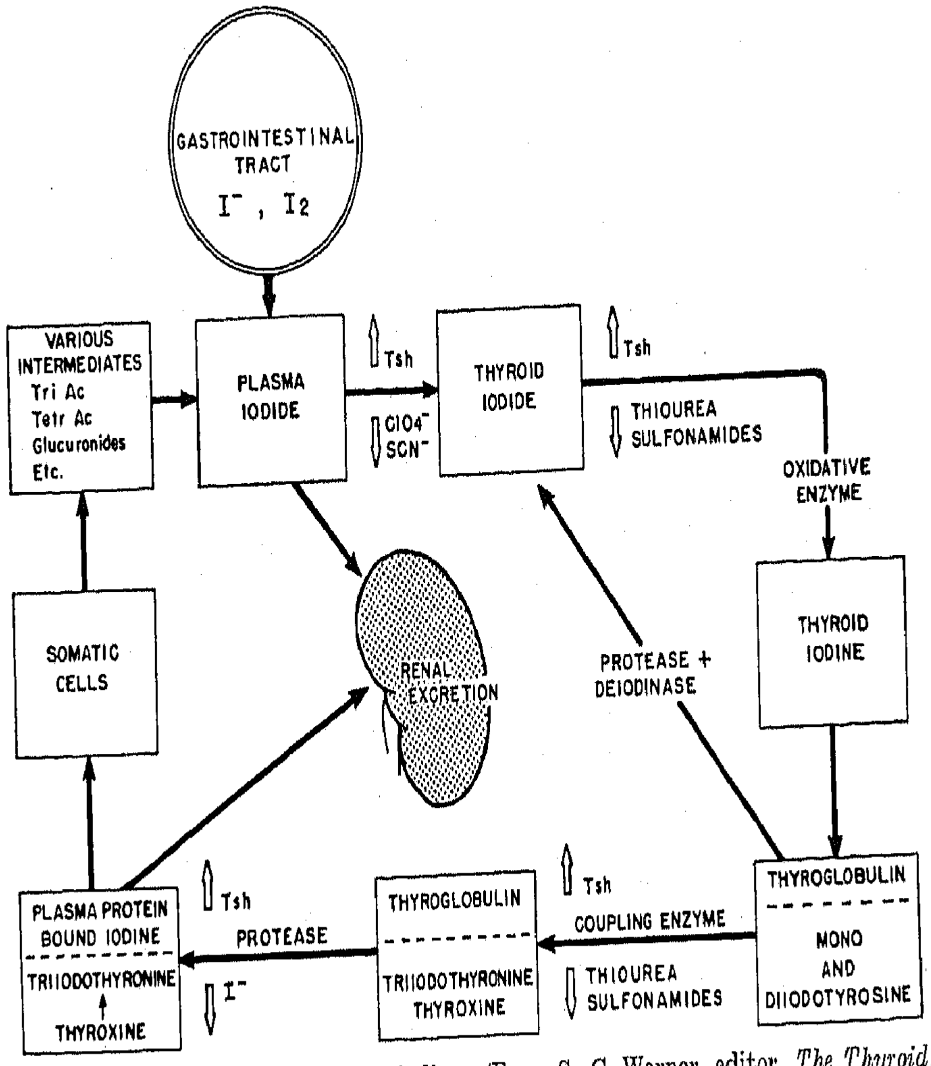


FIG. 55-1. General scheme of iodine metabolism. (From S. C. Werner, editor, *The Thyroid*, Ed. 2, Hoeber Division, Harper and Brothers, 1962.)

The thyroid hormones affect many enzyme systems, as has been demonstrated by numerous investigators. It is difficult, however, to correlate these findings on isolated enzyme systems with the physiologic and pharmacologic responses to these hormones. The interesting work by Lehninger (1956) and his associates has presented a new view of the action of thyroxin at a cellular level. They observed a marked correlation between mitochondria from different tissues that were susceptible to swelling by the action of the hormone, and their increased respiration. For example, they observed that thyroxin produced swelling in mitochondria from liver and kidney, but not in those from the spleen, brain, and testis. In hyperthyroid rats, the liver and kidney showed increased oxygen consumption; the spleen, brain, and testis did not exhibit increased respiratory metabolism.

This work suggests that the mechanism of action of the thyroid hormones on tissue respiration may be achieved by their action on the mitochondrial membrane. The action may facilitate the transfer of substances involved in energy transfer and respiratory activity through the modified mitochondrial membrane. Thus the action of the thyroid hormones may resemble, to a degree at least, the action of insulin in its capacity to "pump" glucose into the cell, making it available for the action of the cellular enzymes.

The increased metabolic rate elicited by thyroid involves increased oxygen consumption without appreciable change in respiratory quotient. All types of foodstuffs are utilized more rapidly. Glycogen is mobilized from the liver into glucose, and an elevated blood sugar level often obtains. Nitrogen excretion is increased, indicating the accelerated rate of protein metabolism. Fat is also oxidized, and animals under thyroid therapy undergo marked losses in body weight.

The increased metabolic rate which is evoked by thyroid must be differentiated from the increased metabolic patterns which are produced by epinephrine, ergonovine, and dinitrophenol. Each of these substances is capable of increasing the basal metabolic rate in normal or thyroidectomized animals. Not any of these substances, however, will alleviate the symptoms of myxedema when administered to a patient with that disease. *The increase in basal metabolic rate induced by thyroxin or triiodothyronine is concomitant with the relief of the symptoms of myxedema.*

In hypothyroid states the cholesterol level of the blood is elevated. When thyroid is administered, the hypercholesterolemia is corrected. Rosenman *et al.* (1951) showed that the hyperthyroid rat excreted more cholesterol in the bile than the hypothyroid rat. Using this measure of cholesterol synthesis, there appears to be an increase in hyperthyroidism, although the plasma levels reveal an opposite picture. The lower plasma level in hyperthyroidism is likely due to increased excretion in the feces and/or increased catabolism of the steroid.

Along with the action of thyroid on the metabolic rate, a *tachycardia* is generally produced. The increased heart rate is not a result of the increased metabolic rate. When dinitrophenol increases the basal metabolic rate in thyroidectomized animals, tachycardia does not occur. When thyroxin is administered to the same animals, the increased basal metabolic rate is accompanied by a quickening of the pulse (Leblond and Hoff, 1944). In animals which are poisoned with thyroxin, the excised heart will beat as much as 50 per cent faster than the normal heart (Andrus, 1932).

It has been demonstrated that in the thyrotoxic rat the vagal impulses to the heart were blocked. As a result of this vagal action the pulse was accelerated. Thus the tachycardia, at least in the rat, appears to involve a neurogenic component. The autonomic effects of thyroid have been recognized for years. Apparently the peripheral nervous system shares the increased activity of other tissue cells. Thyroidectomy diminishes the response of the sympathetics to epinephrine. When thyroid is administered, or in hyperthyroid states, the response of the adrenergic innervated structures to epinephrine is greatly enhanced.

Woodbury *et al.* (1952) showed that thyroxin decreased the electroshock threshold for minimal seizures, indicating increased brain excitability. On the other hand, thyroidectomy and the administration of propylthiouracil increased the threshold, manifesting decreased brain excitability. Thus it is seen that the brain shares the thyroxin-stimulating effect of peripheral nerves and other tissues.

Associated with the increased basal metabolic rate in man there occurs *nervous irritability, restiveness,* and often *palpitation.* After the administration of either thyroid or thyroxin there is a *latent period* of 24 to 36 hours before the effects are manifest. This is also true if the thyroxin is injected intravenously. Upon repeated dosage the full effects are observed in 7 to 10 days. The effects may *continue* for several days or even weeks after the *cessation* of the medication.

Excessive dosage with thyroid or thyroxin produces a syndrome comparable to Graves' disease. There occurs a rapid, irregular pulse with marked palpitation. Headache, muscle pains, tremors of the extremities, profuse sweating, and fever occur. Fatal doses evoke intractable vomiting, coma, and collapse. Chronically, toxic doses produce emaciation.

**Thyroid in mild hypothyroidism.** In mild cases of hypothyroidism the administration of thyroid powder often produces *spectacular improvement.* The basal metabolic rate is low, there is a feeling of chronic fatigue, the extremities are often cold, the nails are brittle, and interest in the affairs of life often wanes. As a rule, the administration of 60 to 180 mg. of thyroid by mouth daily causes an amelioration of the symptoms and a return of the basal metabolic rate to normal. Often a small quantity of *Dexedrine* (*d-amphetamine,* see page 475), 5 to 10 mg. 2 or 3 times a day, is given simultaneously to brighten the spirits by its central stimulation. After the relief of the symptoms the dose of thyroid may be gradually reduced but can seldom be discontinued if there was a definitive need for thyroid when therapy was instituted.

**Thyroid in obesity.** Thyroid is often useful in reducing body weight in obese individuals. It is imperative that the dose be kept small and that the weight reductions be instituted over a *long period* and *not precipitously.* Protein intake in the diet should be increased to compensate for the increased nitrogen excretion.

Edwards and Swyer (1950) compared the effectiveness of thyroid powder in relieving obesity with that of *d*-amphetamine in 24 carefully controlled patients during a 4-month period. The individuals were placed on a diet of 1000 calories per day diet plus 5 mg. of *d*-amphetamine sulfate 3 times a day or 50 mg. of thyroid powder 3 times a day. Those patients receiving *d*-amphetamine showed a significantly greater weight loss than those with the low caloric diet alone. Those receiving the thyroid powder showed no greater weight loss than that produced by the low caloric intake.

There appears to be a definite medical trend away from the use of thyroid in obesity to the use of the amphetamines (see page 475). However, Gelvin *et al.* (1959) used triiodothyronine, 75 μg. daily, with 1000-calorie diets successfully in 57 carefully controlled patients to achieve weight loss. The drug produced no symptoms of hyperthyroidism. They contend that triiodothyronine is of definitive value to patients who do not lose weight on a weight-reducing regimen.

**Thyroid in cretinism.** Cretinism is a congenital form of thyroid insufficiency. Paracelsus called the condition a *toad-like caricature of the human race.* Growth is retarded, the skin is coarse and dry, the expression is imbecile, the speech has a drawl, the tongue is thick, and the intellect is dull.

Osler commented, "Even the magic wand of Prospero or the brave kiss of the daughter of Hippocrates never effected such changes as these" when he referred to the administration of thyroid to a cretin. Indeed, the success of the treatment depends upon the institution of therapy early in life and the faithful maintenance of it. The dosage must be regulated for each case to provide the maximal advantage of the hormone and yet avoid toxic symptoms. Although the child's condition is dramatically improved, most cretin children remain more or less retarded mentally and physically throughout life in spite of treatment (Brown *et al.*, 1939). If a cretin is recognized during the first few weeks of life and thyroid therapy is instituted, mental acuity may reappear and the intellect may develop normally.

**Thyroid in myxedema.** Myxedema is a form of nonpitting edema caused by fibrous changes and gradual atrophy of the acini of the thyroid gland or any other condition which results in the ablation of the thyroid gland. These include total thyroidectomy, excessive dosage of radioiodine, or infiltration of the gland by tumor, amyloid, or the abnormal lymphocytes in Hashimoto's struma. The subcutaneous tissue becomes infiltrated with a mucin-like substance. There is dullness of intellect, staggering gait, impairment of speech, tremors, and muscular weakness. The basal metabolic rate is low. The normal hormonal iodine (protein-bound iodine, PBI) in man is from 4 to 8 μg. per cent in the blood serum. In advanced myxedematous states it is found to be less than 1 μg. per cent. In extreme hyperthyroidism the level may reach 20 μg. per cent.

Thyroid supplies the *necessary cellular stimulus to return the patient nearly to normal.* Thyroid is administered in doses of 60 to 180 mg. daily. In a few days improvement becomes noticeable. The foregoing symptoms begin to disappear, and after 2 or 3 weeks of therapy the patient becomes nearly normal (Means, 1935). Warning symptoms of overdosage are muscle pains and substernal distress resembling angina pectoris. Treatment must be continued. Often the dosage may be decreased during the warmer weather.

**Other uses of thyroid.** As stated previously, thyroid stimulates cellular activity to its *maximal state of energy production.* In many conditions not directly associated with thyroid insufficiency thyroid has been given with varying degrees of success.

Thyroid has been used in the treatment of *hypogonadal function* and *menopausal arthralgias in women* with limited success. Thyroid is also employed in *infertility,* increasing the metabolic rate to 110 or 120 with success in some cases.

The accelerated metabolic function induced by thyroid prevails in the skin, and the substance has had some value in the treatment of *refractory cases of eczema.*

Thyroid powder and the hormones thyroxin and triiodothyronine are used in the treatment of *hypercholesterolemia.*

Aub *et al.* (1929) showed that thyroid administration produces an increase in calcium and magnesium excretion. The mobilization of calcium is believed to affect favorably the *delayed union of fractures.* Silberberg and Silberberg (1939) showed that thyroid increased the bone calcification rate in young animals and *aided in callus formation.*

## FATE OF THYROXIN IN THE BODY

When thyroglobin is injected in the blood it is rapidly broken down, liberating iodide. Furthermore, when thyroxin or thyroid powder is administered, the blood level of iodide returns to normal within 24 hours. It is therefore apparent that neither thyroxin nor the iodide resulting from its decomposition remains in the blood for long periods of time.

After the administration of thyroxin, the hormone is found in comparatively high concentration in the kidney. The urinary iodine excreted, however, is inorganic iodide. Using thyroxin tagged with radioactive iodine, Gross and Leblond (1947) found large quantities of the hormone excreted into the gastrointestinal tract. This was excreted mainly in the bile.

The liver plays an important role in the regulation of thyroid-hormonal activity. This is not limited to its capacity to bind thyroxin with glucuronic acid and excrete it in the bile. In addition, the liver is capable of deiodination and oxidation of thyroxin to triiodothyronine and tetraiodothyroacetic acid, respectively. These processes can be disturbed by liver damage (Vannotti *et al.*, 1957).

Twenty-four hours after the injection of a large dose of thyroxin, as much as 75 per cent of the hormone was recovered from the feces. It therefore appears that the liver and gastrointestinal tract play the major role in the metabolism and excretion of thyroxin, with a minor portion disposed of by the kidneys.

**Thyroid versus thyroxin.** Thyroid powder is generally used in routine hypothyroidism therapy. In the powdered thyroid as administered it had been estimated that about 30 per cent of the iodine present is in the form of thyroxin, 70 per cent is present as diiodotyrosine. The pharmacologic potency of the thyroid powder appears to be a function of its total iodine (in thyroid combination) content. Nevertheless when the diiodotyrosine is separated from the thyroxin, the former is inactive. There remains, however, the possibility of the union of 2 molecules of diiodotyrosine to form thyroxin and also the possible presence of the very active triiodothyronine in the powder. Absorption from the intestinal tract is dependable, and therapy with thyroid powder is not costly.

**Sodium L-Thyroxin** is available in tablets of 0.1 mg. each. The compound appears to be uniformly absorbed to the extent of 50 per cent from the gastrointestinal tract. This is especially true if the tract is quite free of food. The activity of sodium L-thyroxin is approximately twice that of racemic thyroxin administered intravenously (Hart and Maclagan, 1950). Between 0.2 and 0.4 mg. of sodium L-thyroxin orally is the approximate calorigenic equivalent of 120 mg. of thyroid powder. Starr and Liebhold-Schueck (1953) held the view, after treatment of hypothyroid patients with sodium-L-thyroxin, that this product was comparable in all respects to thyroid powder. In addition, its use obviated the variability of response produced by some of the commercial thyroid powders.

**Triiodothyronine, Cytomel.** Frawley *et al.* (1956) used triiodothyronine in 13 myxedematous patients and confirmed clinically that the response elicited was identical with the action of thyroxin. The potency of the former is greater. The side effects observed did not differ qualitatively from those evoked by other thyroid preparations. These investigators caution that the more potent thyroid products such as triiodothyronine may place an additional burden on the cardiovascular system of the patient. Indeed, they observed angina pectoris and congestive heart failure after instituting treatment in certain of their patients. The symptoms were ameliorated by dosage reduction. The overall advantage of this more potent agent over thyroid powder in the treatment of hypothyroid states remains to be established.

L-Triiodothyronine is available under the name of Cytomel in tablets containing 5 and 25 $\mu$g. The usual daily replacement dose with L-triiodothyronine orally appears to be about 75 $\mu$g.

In the treatment of myxedema, the administration of thyroid elevates the PBI to normal levels. With thyroxin the PBI is likely to be elevated to levels higher than normal when the dosage is adequate. On the other hand, when triiodothyronine is used, the PBI rises only slightly and remains at subnormal values even when the replacement therapy is adequate. Triiodothyronine is bound by plasma proteins, probably the alpha globulins; its low level in the plasma may be due to its rapid disappearance into tissue spaces (Selenkow and Asper, 1955).

**Thyroxin analogs.** The value of the thyroid hormones in hypercholesterolemia appears to be established. Effort has been made to substitute thyroxin analogs for thyroxin in order to lower serum cholesterol without concomitant effects on the metabolic rate. Among the compounds studied are tetraiodothyroacetic acid, triiodothyroacetic acid, diiodothyroacetic acid, tetraiodothyroformic acid, and triiodothyropropionic acid. Herrmann *et al.* (1961) showed that thyroacetic acid derivatives were less active relative to their toxicity in reducing the serum cholesterol level in rats than were their corresponding thyroformic acids.

These compounds appear to be capable of lowering the serum cholesterol level about 20 per cent without appreciable action in elevating the metabolic rate. However, frequently with treatment pre-existing angina pectoris was aggravated and exercise tolerance was reduced. Nichols (1962) used triiodothyropropionic acid (Triopron) in dosage levels of 3 mg. daily in primary hypercholesterolemia with xanthomatosis successfully in several cases. The calorigenic effect of the analog was not a complicating factor.

## THYROTOXICOSIS, IODINE, AND ANTITHYROID COMPOUNDS

The etiology of thyrotoxicosis has not been established. Excessive stimulation of the thyroid gland by the thyrotropic hormone might be responsible, although it may be caused by autonomous excess secretion of the thyroid hormones by the thyroid gland. It appears that psychic trauma, infection, or injury might precipitate the disease. The classic signs and symptoms of the disease are *exophthalmos, goiter, tremor, nervousness, irritability, sweating,* and *hyperkinesis. Loss of weight and strength* are also usual findings.

### Inhibition of thyroid hyperactivity.

The 2 principal pharmacologic means of depressing the activity of the thyroid gland are by the administration of radioactive iodine or the antithyroid drugs. Other methods of lesser importance involve the administration of iodides, thiocyanates, or perchlorates. Surgical ablation of a portion of the gland or exposure to x-ray are other procedures used to diminish the hyperactivity of the thyroid gland.

### Radioactive iodine in hyperthyroidism.

Radioactive iodine ($I^{131}$) has been employed very successfully in the treatment of hyperthyroid states. Sodium radioiodide and its solution are official in the Pharmacopeia. The activity is expressed in millicuries. The solution may be given orally or intravenously. Diagnostically the dose is 1 to 100 $\mu$c., and therapeutically, 1 to 100 mc.

Feitelberg and his associates (1950) treated 300 patients in various states of hyperthyroidism with radioactive iodine. Many of the patients had adenomas. In each case the size of the thyroid gland was estimated by 3 observers. Based on this estimated size of the gland and the measured excretion of a tracer dose, radioactive iodine was administered in quantities to deliver approximately 10,000 units roentgen equivalents to the gland. This amount expressed in $I^{131}$ was 8.2 mc. on the average. The half-life period of $I^{131}$ is about 8 days. All of the patients except 2 were cured by the treatment. The subsequent administration of Lugol's solution appeared to be necessary in only 7 of the cases. Thirteen of the patients developed hypothyroidism, which had to be treated with thyroid powder. The distribution of $I^{131}$ is shown in Fig. 55-2.

There have been many encouraging reports establishing radioactive iodine as an acceptable agent in the treatment of hyperthyroidism. For example, McCullagh (1956) states that "Among the advantages of $I^{131}$ therapy in Graves' disease are: mortality is zero, no permanent tetany, control is complete in almost 100 per cent of the cases, there is no discomfort, and recurrence is almost unknown." Since the appearance of McCullagh's enthusiastic statement, a few deaths have been reported sequential to the use of radioiodine. Destruction of the gland was so rapid that fatal exacerbation of the hyperthyroidism occurred.

Kennedy and Fish (1959) reported 6 cases of leukemia resulting from the use of radioiodine in the treatment of hyperthyroidism. This is a serious sequela to treatment, and caution is therefore to be employed in the use of radioiodine in patients in whom the antithyroid drugs might serve with equal efficacy. Werner *et al.* (1961) made an interesting follow-up study of the incidence of leukemia following the treatment of thyrotoxicosis with radioactive iodine. In their series from various clinics, in which 32,000 cases were followed for 142,000 person-years, there were 10 cases of leukemia. This number does not exceed the number of expected cases of the disease, based upon persons untreated with $I^{131}$ with sex and age considered. Thus the issue is not closed, and further follow-up studies will be necessary to clarify the problem.

Radioactive iodine has been used with success in intractable cases of angina pectoris. Albright *et al.* (1958) are of the opinion that when routine standard therapy has been exhausted the treatment of angina pectoris with radioactive iodine is as efficacious as the surgical ablation of a segment of the thyroid gland. They obtained excellent results in 29 of 58 patients so treated.

Radioactive iodine is used diagnostically to determine the functional activity of the thyroid gland. Jaffé and Ottoman (1950) used radioactive iodine to determine hyperthyroid states. The capacity of the gland to remove the radioactive element from the blood was the criterion. They claim an accuracy of 95 per cent for the tracer test. This they compare with an accuracy of 67 per cent for the basal metabolism test.

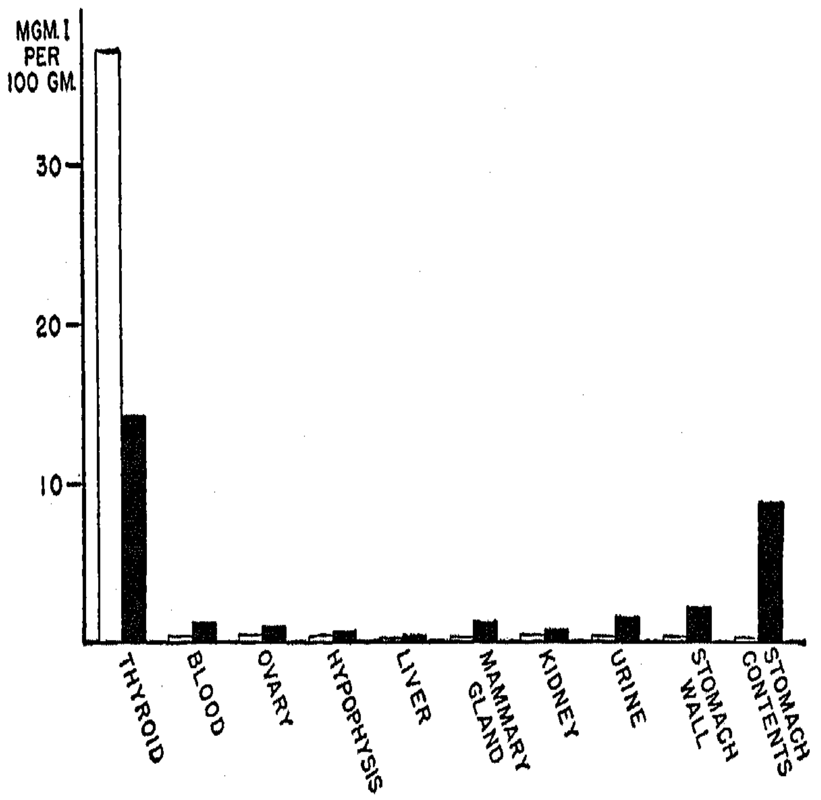


FIG. 55-2. The *solid columns* represent the amount of a pharmacologic dose of radioiodine entering the various organs. The *light columns* represent the total iodine (values taken from the literature). (From C. P. Leblond, Recent Progr. Hormone Res., **3**: 159, 1948.)

Silver *et al.* (1955) caution against complete dependence on the radioactive iodine test for thyroid activity. False positive results may be obtained in euthyroid patients, thus subjecting them to surgery or treatment with $I^{131}$.

In Silver's studies several euthyroid individuals showed hyperthyroid $I^{131}$ uptakes. The results of the studies suggest confirmation of laboratory findings by determination of the protein-bound serum iodine value (PBI) and basal metabolic rate and consideration of the clinical condition of the patient.

Hamolsky *et al.* (1957) developed a simple test for the functional activity of the thyroid gland. They employed $I^{131}$-labeled L-triiodothyronine, using the red blood cell uptake of the hormone *in vitro* as a criterion. It is clear that such a test does not require the presence of the patient, nor does it expose him to radioactivity. All that is required is the reagent and 10 ml. of oxalated blood from the patient. After appropriate treatment with the radioactive hormone the cells are separated from the plasma, and the ratio between the radioactivity of the washed red blood cells and the whole blood is determined by a scintillating counter. The red cell uptake of triiodothyronine is decreased in hypothyroidism and increased in hyperthyroidism.

A simplified modification of the test has been devised, based upon the principle that triiodothyronine $I^{131}$ is effectively taken up by and bound to Triosorb resin sponge (polyurethane resin-embedded sponge). The relative binding of radioactive triiodothyronine added to the patient's serum by the serum and Triosorb sponge is the basis for diagnosis. In hypothyroidism the primary binding sites for triiodothyronine $I^{131}$ are relatively unsaturated. The binding or uptake by Triosorb sponge is decreased in hypothyroidism and increased in hyperthyroidism (Mitchell *et al.*, 1960).

### The antithyroid drugs.

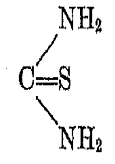
An important development in the treatment of hyperthyroidism has been the discovery of the *antithyroid drugs*. These substances, such as thiourea and thiouracil, block thyroid action by preventing the oxidative union of iodine with the tyrosyl groups (Astwood *et al.*, 1945).

There are 2 oxidative mechanisms occurring in the thyroid gland which convert iodine into thyroxin. The first, which appears to be the more rapid, is the iodination of tyrosine. The second, which proceeds more slowly, is the coupling of 2 of the diiodotyrosine molecules to form thyroxin. When the second reaction occurs, a molecule of alanine is set free which ultimately breaks down into pyruvic acid and ammonia. It appears that the thyroid cells exhibit peroxidase activity which catalyzes the oxidations (DeRobertis and Grasso, 1946). The 2 reactions may occur in the cells of the thyroid gland. However, the formation of thyroxin may occur also in the colloid matter of the more active follicles. *It appears that both of these reactions are blocked by the antithyroid drugs, as shown in* Fig. 55-1.

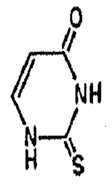
The historical development of the antithyroid compounds goes back to the observation of Mackenzie *et al.* (1941). These investigators found that sulfaguanidine evoked hyperplasia of the thyroid gland when given to rats. The hyperplasia was not checked by the administration of iodides but was controlled by the giving of thyroxin. Grant and Krantz (1942) studied a number of urea and thiourea derivatives on the oxygen uptake of tumor tissue and normal tissue by the Warburg technic. They observed that guanidine, thiourea, and several derivatives of the latter compound markedly depressed the oxygen consumption of excised tissues.

Astwood and his associates (1943 *et seq.*) showed that when thiourea, and to a greater degree thiouracil, was administered to animals and man, it possessed marked action in depressing thyroid function. The prolonged feeding of thiouracil to rats was observed to produce cretinism (Hughes, 1944).

The structures of thiourea and thiouracil are shown in the formulas below.



Thiourea



Thiouracil

Since the discovery of the antithyroid activity of thiouracil, hundreds of compounds have been screened for their antithyroid activity. Astwood *et al.* (1945) published a survey of more than 300 compounds which have been studied for this purpose. The evaluation of the compounds is carried out by determining the *dose needed to reduce the thyroid iodine of the white rat to 12 mg. when compared with the activity of thiouracil in this respect* (McGinty and Bywater, 1945).

McGinty and Bywater (1945) found antithyroid activity among the chemotherapeutically active sulfones. Promizole (see page 168) was 18 per cent as active as thiouracil, whereas its sulfide was 53 per cent as potent.

Certain aniline derivatives such as the sulfonamides and the aminobenzoic acids also exhibit antithyroid activity. Their potency, however, does not compare favorably with that of thiouracil.

It appears that the thiouracil structure produced maximal antithyroid activity. Therefore, an effort has been made to obtain derivatives of this nucleus more potent than thiouracil and devoid of undesirable untoward action. The outstanding toxic manifestation of thiouracil therapy is *agranulocytosis*. The relative potency of those derivatives having substituent groups in position "6" were studied. It was found that 6-*n*-propylthiouracil has the greatest potency of any of the substituted thiouracils tested. No other compound of this type tested by Astwood equaled it. In clinical use, propylthiouracil has been found to be 3 or 4 times as potent as thiouracil, in contrast to the 11 : 1 ratio in rats. The incidence of side effects with propylthiouracil is, however, only a fraction of that with thiouracil.

Propylthiouracil has become the antithyroid drug of choice of this series. The incidence of untoward side effects from propylthiouracil in 931 cases was found to be 2.8 per cent, as compared with 13.1 per cent with thiouracil (Van Winkle *et al.*, 1946). Of striking importance is the fact that *agranulocytosis occurred in 2.5 per cent of the cases with thiouracil and in only 0.1 per cent with its propyl derivative.*

**Propylthiouracil, U.S.P.** Propylthiouracil occurs as a white, crystalline or powdery substance. It elicits a bitter taste. The substance is very slightly soluble in water. It is available in 50-mg. scored tablets.

*Propylthiouracil in hyperthyroidism.* When propylthiouracil is fed to laboratory animals, the food consumption diminishes, the basal metabolic rate is lowered, growth is retarded, and histologic changes are produced in the pituitary gland similar to those caused by thyroidectomy. Hyperplasia and enlargement of the thyroid gland occurs. The thyroid gland changes do not occur in hypophysectomized animals. It appears therefore that *the action of propylthiouracil is direct upon the thyroid gland, blocking thyroxin synthesis.* The hyperplasia of the gland is a secondary effect due to pituitary hyperactivity induced by diminished thyroxin secretion.

Propylthiouracil is rapidly absorbed from the gastrointestinal tract. Its action is prompt and extends over a longer period of time than that of thiouracil.

Clinically, propylthiouracil is used (1) to pre-

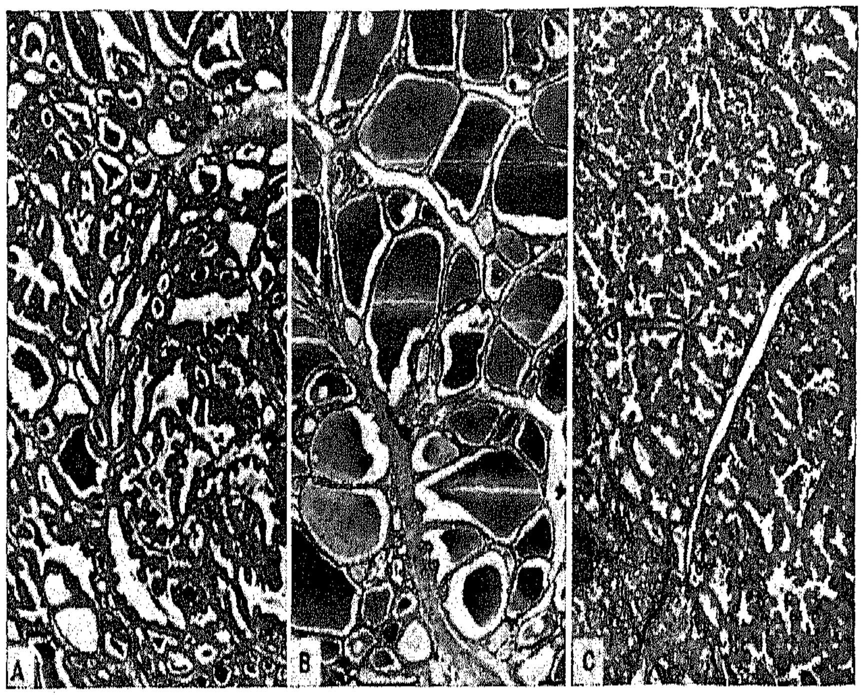


FIG. 55-3. *A*, Section of thyroid gland of patient with untreated Graves' disease; *B*, Graves' disease treated with potassium iodide for 3 weeks; *C*, Graves' disease treated with thiouracil for 5 weeks. Note that the iodized gland has more colloid and less hyperplasia than the others, whereas the reverse is true of the thiouracillized gland. Such differences, however, do not invariably exist. (From R. H. Williams, J. Clin. Endocrinol., 6: 1, 1946.)

pare a patient for thyroidectomy, and (2) in medical treatment as a substitute for thyroidectomy.

The dose of the drug is 100 to 350 mg. daily: occasionally a greater dosage level is required. The dose is usually divided into 3 portions and administered at 8-hour intervals. The tablets contain 50 mg.

The use of propylthiouracil produces distinct improvement in the patient's condition within 10 days; however, several months may be required for remission to occur. The diminution of basal metabolic rate is concomitant with the clinical changes in thyrotoxicosis.

The changes in the histologic picture of the thyroid gland are shown in Graves' disease, and after thiouracil and iodide treatment, respectively, by Williams (1946) (fig. 55-3).

Williams (1946) is of the opinion that the best results in the treatment of thyrotoxicosis are achieved by the use of an *antithyroid drug and iodide.* In preparing the patient for surgery, iodine and propylthiouracil decrease the *vascularity* and *sponginess* of the gland. Propylthiouracil alone does not accomplish this.

The advantages of propylthiouracil therapy in hyperthyroidism are as follows:

1. It is effective and relatively safe;
2. It is relatively inexpensive;
3. It has little morbidity and practically no mortality;
4. There are no secondary complications;
5. It is better for areas without skilled thyroid surgeons;
6. It avoids an operation.

The advantages of treatment of thyrotoxicosis with antithyroid drugs have been cited. Of these, at present propylthiouracil seems to offer the greatest advantages with the least untoward effects. *Drug fever, simple leukopenia and neutropenia, skin rashes,* and *urticaria* have been observed occasionally when propylthiouracil is administered. As stated, however, the incidence of *agranulocytosis* is very low. Deficiency of *prothrombin* and *proconvertin* have been observed after propylthiouracil therapy in several patients. Kolars and Gonyea (1959) reported a case and reviewed several others which have been encountered. The hemorrhagic diathesis was checked by the administration of phytonadione (see page 698). In the preparation of the patient for surgery there appears to be an advantage in the use of combined propylthiouracil and iodide therapy.

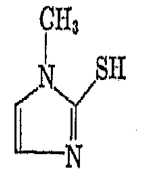
Propylthiouracil has caused goiter in the fetus when administered to the mother in large doses. It appears that if the dosage level is minimal this can be avoided.

**Methylthiouracil, U.S.P.,** is a popular antithyroid drug in England. The compound appears to be slightly more potent and slightly more toxic than propylthiouracil. The usual dose is 50 mg. 4 times daily.

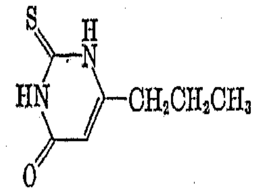
In order to achieve the decrease in vascularity and sponginess of the thyroid gland prior to surgery without recourse to additional iodide therapy, sodium 5-iodo-2-thiouracil is often used. The compound, known as *Itrumil,* is a typical antithyroid drug with iodine in the molecule. Itrumil shows a low incidence of side effects. It is administered in daily divided doses of 150 to 300 mg. Tablets are available containing 50 mg. of Itrumil.

In severe cases of hyperthyroidism reserpine serves well as adjunctive therapy to the antithyroid drugs. It tranquilizes the patient and slows the heart rate, while the full effect of the antithyroid drug is accomplished. It has been shown by Bierwagen and Smith (1959) that reserpine evokes a depression of thyroid activity which is probably mediated through its effect on the release of thyrotropin by the pituitary.

**Methimazole, U.S.P. (Tapazole).** Stanley and Astwood (1947) studied a large number of antithyroid drugs by the radioactive iodine technic. One of the compounds studied appeared to exhibit marked antithyroid activity in very small dosage schedules. The compound is known as *methimazole,* which is 1-methyl-2-mercaptoimidazole. The relation of methimazole to propylthiouracil is shown in the accompanying formulas.



Methimazole, U.S.P.



Propylthiouracil, U.S.P.

Methimazole occurs as a white to pale buff, crystalline powder. It is readily soluble in water. When fed to laboratory animals methimazole exhibits approximately the same degree of toxicity as does propylthiouracil. However, its antithyroid activity is from 10 to 20 times that of propylthiouracil. The over-all action of methimazole is similar to that of propylthiouracil. The response is a function of the dose, the size and consistency of the patient's thyroid gland, and of whether or not iodine therapy has been employed.

Irwin and Van Vactor (1952) made a comparative study of the 2 drugs in about 100 patients with hyperthyroidism. About half the number were treated with methimazole and half with propylthiouracil. The average daily dose was 39 mg. with methimazole and 355 mg. with propylthiouracil. Immediately one observes that these investigators found methimazole about 10 times as potent as propylthiouracil. Methimazole was found to be more prompt in eliciting a response than propylthiouracil. The incidence of toxicity appeared about the same in each group.

Our impression is that methimazole is an extraordinarily useful drug in hyperthyroid states. However, as with propylthiouracil therapy, the danger of serious blood dyscrasias should always be considered as a possible hazard of therapy. Croke and Berry (1952) noted a case of agranulocytosis in a woman 65 years of age during methimazole therapy. Methimazole is available in 5-and 10-mg. tablets. It appears from various clinical studies that the incidence of agranulocytosis and drug fever elicited by methimazole and propylthiouracil is about the same. Other toxic manifestations of methimazole therapy reported are neuropathy with foot drop (Accetta *et al.,* 1954) and loss of sense of taste (Hallman and Hurst, 1953).

### Iodides in Hyperthyroidism

For many years in the routine treatment of thyrotoxicosis iodine and iodides have been employed. Lugol's solution, 0.3 to 0.6 ml. diluted with water, containing iodine and potassium iodide, has been a favorite preparation. Certain organic iodine compounds have been used which appear to supply iodine with less concomitant gastrointestinal distress than does Lugol's solution.

Several clinical investigators in recent years have pointed out that Lugol's solution should be administered to hyperthyroid patients only after most careful consideration, for it has certain disadvantages:

1. The patient who has had Lugol's solution cannot be immediately treated with radioactive iodine because the body and the gland are "saturated" with iodide and the gland, therefore, will have no affinity for radioactive iodine.

2. Even if Lugol's solution is withdrawn and radioactive iodine is given later, an exacerbation of hyperthyroidism may be induced because of the rapid destruction of the involuted gland. Iodide causes the gland to store its hormone, and if such a gland is destroyed by radiation with $I^{131}$, this

hormone is released into the circulation and severe thyrotoxicosis may ensue.

3. If Lugol's solution is given first and later propylthiouracil or methimazole is administered, an exacerbation of hyperthyroidism may occur (Prout and Asper, 1958).

Iodides cause a *temporary reversal of the hormonal secretion which is used for the preparation of the patient for surgery.* During this period of remission of many of the symptoms, the hormone flows into the empty follicles of the gland instead of into the blood (Salter, 1944). Proteolysis of the thyroid colloid substance does not occur during the beneficial phase of iodide therapy in hyperthyroidism. DeRobertis and Nowinski (1946) observed that the proteolytic enzyme derived from the thyroid follicle is inactivated by treatment with iodine. Riggs *et al.* (1942) showed that when Lugol's solution is administered in thyrotoxicosis, concomitant with the fall in basal metabolic rate, the PBI will become extraordinarily high. With the administration of the solution a portion of the iodide ingested becomes bound to plasma protein. This, however, is obviously not iodine in thyroid combination. During therapy with Lugol's solution, the iodine in thyroid combination *per se* diminishes; this is butanol-extractable iodine (BEI). In most patients PBI and BEI are identical or nearly so, but this does not prevail when Lugol's solution is administered.

It is possible that iodides also inhibit the pituitary gland and exert their action by this mechanism. As a rule the improvement is temporary, the hormone present in the gland is secreted again into the blood, and the disease undergoes exacerbation. The complete explanation of this "escape phenomenon" is at present lacking. However, Means and his associates (1928) suggest that iodides given in therapy (unphysiologic quantities) always exert an inhibitory influence on thyroxin secretion. It is possible that this offers an explanation for the prolonged beneficial results obtained by some patients with mild hyperthyroidism using iodides.

Iodides cross the placental barrier and are taken up by the fetal thyroid gland after about the 12th week of gestation. It is clear that radioactive iodine is interdicted in pregnancy. Indeed, repetitious doses of iodides are also contraindicated such as the use of iodides in the treatment of asthma. Goiters of sufficient magnitude to cause respiratory arrest after birth may develop in the fetus.

Certain anions such as thiocyanate, periodate, and perchlorate are capable of evoking hypothyroidism. Perchlorate is the most potent and is used to a limited extent in the treatment of hyperthyroidism. It appears that the perchlorate ion ($ClO_4^-$) releases the iodide stored in the thyroid gland and further prevents its concentration. The synthesis of the thyroidal hormones is not directly thwarted by perchlorate. It is the relative deficiency of iodide in the gland that reduces thyroxin synthesis. The thyroxin deficiency stimulates the secretion of the thyroid-stimulating hormone, and this in turn elicits thyroid hyperplasia. The action of perchlorate on the thyroid gland is readily reversible and disappears in about a week after the withdrawal of the perchlorate. The antithyroid activity of potassium perchlorate is nullified by the administration of iodides. This does not prevail with thiouracil therapy, as the mechanism of action of the 2 is different.

### Perchlorates and cobalt salts as antithyroid drugs.

Potassium perchlorate is an effective salt in the treatment of hyperthyroidism. It is especially useful in those patients in whom adverse side effects are encountered with propylthiouracil and methimazole. The response to potassium perchlorate is slower than that to the classical antithyroid drugs. The salt is usually given in equal doses of 600 to 1000 mg. daily in solution at 8-hour intervals. The sodium salt is also employed, and this salt enjoys greater water solubility than does the potassium salt. Side effects often encountered are nausea and skin rash (Morgans and Trotter, 1954).

Krevans *et al.* (1962) reported a case of fatal aplastic anemia following the use of potassium chlorate in thyrotoxicosis.

It has been shown that cobalt salts exert a specific toxicity to the cells of the thyroid gland. Pitmentel-Malaussena and Roche (1958) treated 8 cases of hyperthyroidism with oral cobaltous chloride. The salt was given orally in 1 per cent solution in 3 divided doses after meals; the daily intake varied from 150 to 300 mg. In 4 patients there was marked clinical improvement and evidence of the blockade of thyroxin synthesis; 3 of these cases went to surgery, and the gland presented the histologic appearance of follicular hyperplasia; 1 of the 4 patients was treated for 117 days with cobalt with apparent clinical remission of the disease. In the remaining 4 cases

cobalt therapy was not adequate or was completely ineffective.

Cobalt salts used in combination with iron therapy in secondary anemia have induced goiter in children treated for anemia.

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# *Calcium-Phosphorus Metabolism and Calciferol and Parathyroid Hormone*

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Calcium is a ubiquitous element in the earth's crust. Living tissues share this omnipresence of calcium. Aside from the role that calcium plays in the forming of the skeleton, approximately one per cent of the body's calcium is not in bone. It is present in all tissues and cells and is essential for the maintenance of life.

## Functions of calcium.

1. Calcium is essential for the ossification of *bone* which consists primarily of tricalcium phosphate $Ca_3(PO_4)_2$. Calcium is essential for the formation of teeth and the maintenance of good dentition.
2. Calcium serves as a constituent of the *intercellular cement.* Chambers and Zweifach (1940) have shown this by tissue culture technic. Well-developed sheets of epithelium from embryonic kidney and other organs, when washed with a calcium-free fluid, become loosened from each other. A calcium-rich fluid restores the integrity of the cement material. Calcium likely acts in fixing the cement by converting it into a nondispersable complex.
3. Calcium is essential for *selective cellular permeability*. It is believed that the individual cell has its membranous coating stiffened by calcium. This stiffening of the membrane diminishes permeability. Calcium appears also to be involved in the selective absorption of sugars from the gastrointestinal tract.
4. Calcium is essential for the clotting of blood, page 696.
5. Calcium is necessary for the control of the *excitability of nerve centers.* A diminution of the calcium concentration in the blood produces marked central nervous system excitability. The marked central nervous system depression produced by a high concentration of magnesium in the blood is effectively antagonized by calcium (Auer and Meltzer, 1908).
6. Calcium is necessary for the maintenance of the *rhythm*, *tonicity*, and *contractility of the*

*heart.* The calcium ion antagonizes the toxic action of excessive sodium and the inhibitory action of potassium on the perfused heart. The absence of calcium in the perfusion fluid promptly brings the heart to standstill.

7. Calcium is essential for the contracting of skeletal and smooth muscle. The calcium ion activates the enzyme adenosine triphosphatase, which causes the breakdown of adenosine triphosphate (ATP), releasing energy from the high energy phosphate bonds of ATP.

**Calcium requirements.** The daily calcium requirements for man are between 0.5 and 1.5 gm. These requirements vary with age and growth. Calcium requirements are especially high during lactation and pregnancy. About 30 per cent of the calcium ingested by man is absorbed. The remainder is excreted in the feces. Efficient absorption of calcium by the intestinal mucosal cells cannot be achieved unless the calcium is available in a soluble form to present calcium ions. Hence, the diminution of intestinal alkalinity and the ingestion of citrate which chelates calcium will promote intestinal absorption. A vital agent in the promotion of the absorption of calcium from the intestine is the presence of vitamin D, page 901.

Alcock and Macintyre (1962) showed that the transport of calcium and magnesium ions across the intestinal wall share a common mechanism. Thus in the rat, calcium absorption was increased by a diet deficient in magnesium. Urinary excretion of calcium is decreased in magnesium-deficient rats, which may indicate increased tubular reabsorption of calcium.

The excess of absorbed calcium is excreted in the urine, mainly as calcium phosphates. From 0.1 to 0.4 gm. of calcium is excreted daily in the urine, dependent upon the dietary intake. Calcium salts injected intravenously are almost quantitatively excreted by the kidney in the urine.

**Calcium in the blood.** In normal individuals the calcium content of the blood serum varies from 10 to 10.5 mg. per cent or about 2.5 mM/L. The calcium present in the blood is in 2 distinctly different forms. First, the *non-diffusible calcium* which is chemically bound to serum proteins. Second, the *diffusible calcium* which constitutes about ½ of the total calcium is present as undissociated phosphate and carbonate salts and ionic calcium. The ionic calcium is from 3 to 4 mg. per cent. The various forms of calcium are in equilibrium with each other.

Neuman and Neuman (1958) give the distribution of calcium in the serum as follows in mM per L.: total 2.5, protein bound 0.82 (to globulin 0.17, to albumin 0.65), soluble complexes 0.30, and ionic 1.33.

Occasionally the calcium-serum levels rise in infancy to unusually high levels, giving rise to dire symptoms. This condition is known as idiopathic hypercalcemia (Fraser, 1961).

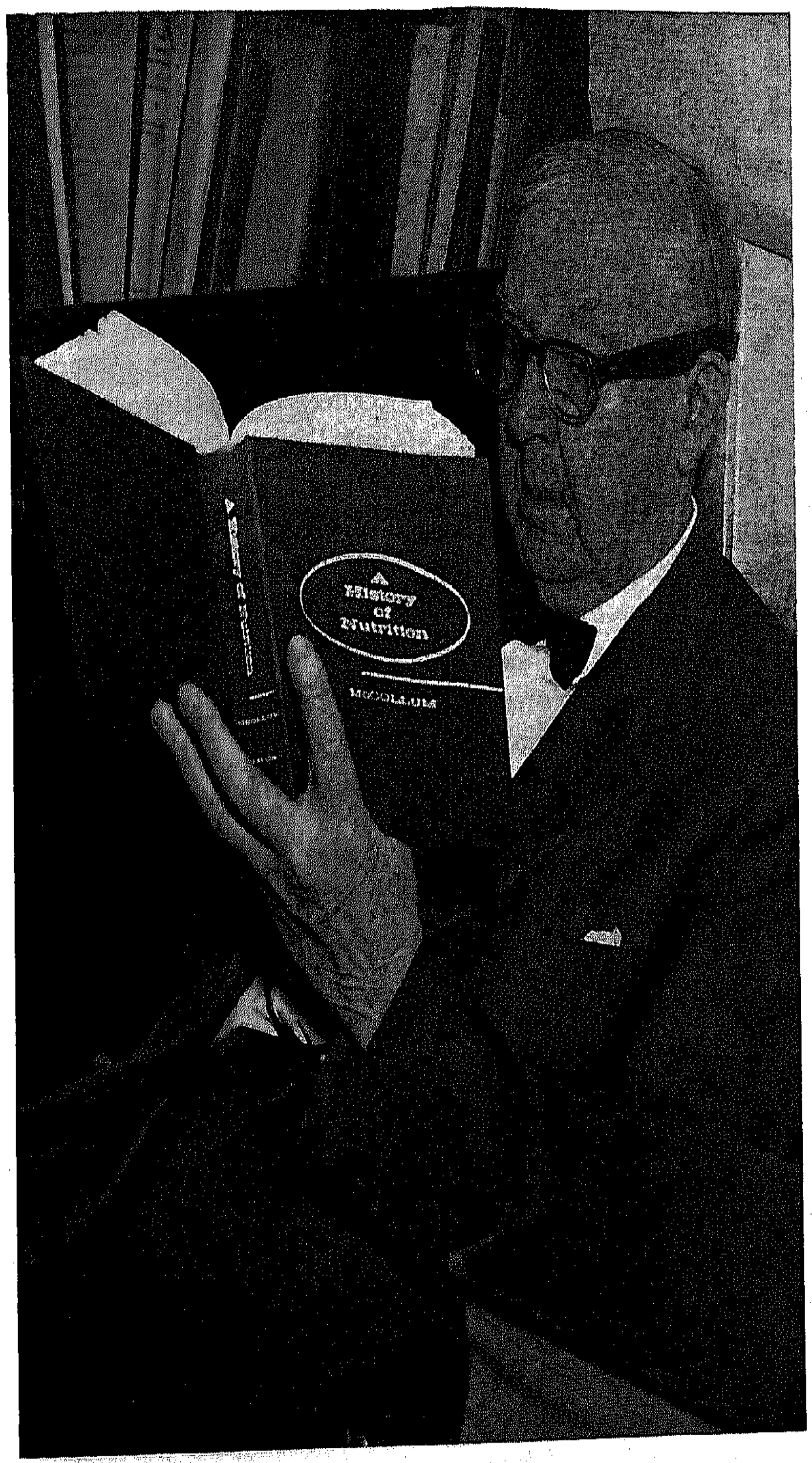
**Alterations in blood calcium level.** Under most conditions the calcium level of the blood remains remarkably constant. The vast supply of calcium reserve in the skeleton can be partially mobilized by the hormone secreted by the parathyroid glands. Low-calcium diets over extended periods of time tend to lower the level of calcium in the blood.

During the latter months of pregnancy the serum calcium is often diminished if the diet is inadequate.

Soluble alkali salts whose acids form insoluble calcium salts, when administered in large quantities, tend to produce hypocalcemia. Citrates, fluorides, and oxalates fall into this class. Phytic acid, which is a phosphorylated inositol and present in brown flour, may diminish the calcium stores of the body if ingested in large quantities for long periods of time. The phytic acid salts of calcium and magnesium are insoluble. The administration of large amounts of sodium phosphate, especially $Na_2HPO_4$, will produce *hypocalcemia.* This is mediated through the combination of the phosphate ion with calcium to form insoluble tricalcium phosphate $Ca_3(PO_4)_2$. The distribution of the ions of orthophosphate in serum are given by Neuman and Neuman (1958) as follows: 18.6 per cent as $H_2PO_4^-$; 81.4 per cent as $HPO_4^{=}$. The proportion of the $PO_4^{\equiv}$ ions is negligible, namely, 0.008 per cent.

Acid favors the formation of the soluble monocalcium phosphate. Alkali and soluble phosphates favor the production of the insoluble type of calcium salt, namely, tricalcium phosphate. Acidotic salts such as ammonium chloride, page 896, will mobilize calcium. In alkalosis the ionic calcium of the plasma is diminished.

In addition to being in ionic equilibrium with the phosphate ion, calcium is in equilibrium with the carbonate ion. Calcium carbonate, $CaCO_3$, is insoluble but solubilized by the addition of $CO_2$



E. V. McCOLLUM

*Distinguished investigator in the field of nutrition, who isolated vitamins A and D*

"The right kind of a diet is the most important single factor in promoting health. It is the material with which to build the foundation for success."

to the solution forming $Ca(HCO_3)_2$. The following equilibrium equation possibly represents the ionic relationships between calcium and the ions of phosphoric and carbonic acids. It shows also the mobilizing effect of increasing the *hydrogen-ion concentration* on calcium.

$$\frac{[Ca^{++}][HCO_3^-][HPO_4^=]}{[H^+]} = K$$

Acid residues in the diet promote the absorption of calcium salts from the gut. Likewise, increased gastric acidity favors the absorption of calcium salts.

There is a small but definite diminution of the serum calcium level in rickets.

Hypercalcemia occurs in *hyperparathyroidism.* The calcium level of the serum may be temporarily increased also by the oral or intravenous administration of calcium salts such as calcium gluconate or calcium lactate.

**Parathyroid hormone and calcium deficiency.** The parathyroid glands were recognized first as separate structures by Sandstrom in 1880. He gave them the name parathyroids because of the belief that they were remnants of embryonic thyroid tissue. Their origin, however, has been shown to be independent of the thyroid gland. The parathyroid glands in man weigh between 100 and 200 mg.

MacCallum and Voegtlin (1909) were the first to show that in the parathyroidectomized dog the calcium level of the plasma invariably was reduced. This reduction of calcium produced the symptoms of *tetany.* They demonstrated further that the tetany could be immediately abolished by the intravenous injection of soluble calcium salts. Hypocalcemia was established as the primary cause of tetany.

Collip (1925), in a series of brilliant investigations, succeeded in obtaining from the parathyroid glands an extract which upon intravenous or subcutaneous administration would elevate the serum-calcium level of parathyroidectomized dogs. Collip's extract was prepared from the glands by extracting with hot diluted hydrochloric acid. The extract was cooled and neutralized to pH 8 with sodium hydroxide. Hydrochloric acid was added to effect a maximal isoelectric precipitation of protein. The precipitated protein was removed by centrifugation and filtration. The clear filtrate contained the parathyroid hormone.

**Parathyroid Injection, U.S.P.** This is a "sterile solution in water for injection of the water-soluble principle or principles of the parathyroid glands which have the property of relieving the symptoms of parathyroid tetany and increasing the calcium content of the blood serum in man and other animals. One ml. of parathyroid injection possesses a potency of not less than 100 U.S.P. parathyroid units, each unit representing 1/100 of the amount required to raise the calcium content of 100 ml. of the blood serum of normal dogs 1 mg. within 16 to 18 hours after administration." The usual intramuscular dose of the preparation is 40 units every 12 hours.

**Effect of parathyroid injection.** The repeated administration of parathyroid hormone to a normal dog produces a series of changes in the blood and gastrointestinal tract. In herbivorous animals these changes are not so pronounced.

1. There is an increase in serum-calcium to 18 or 22 mg. per cent. This appears to be due to the mobilization of calcium from the tissues and bones.
2. The rise in serum-calcium produces *anorexia, weakness, depression, polyuria, vomiting,* and *diarrhea.*
3. Later there is a sharp rise in the serum phosphates and nonprotein nitrogen, and hemoconcentration occurs.
4. *Emesis of bloody fluid, renal failure, prostration,* and *death* follow. At autopsy the gastrointestinal tract is seen to have undergone extensive hemorrhage.

**Mechanism of parathyroid hormone action.** Evidence indicates that the secretion of the parathyroid hormone is controlled mainly by the calcium ion concentration in the serum and extracellular fluid. This is essential as cardiac, neuronal, and muscle activity is affected by slight changes in calcium ion concentration. Phosphate ion concentrations are secondarily influenced owing to the reciprocal relationship between the concentrations of the 2 ions imposed by the solubility of bone mineral.

Manunta *et al.* (1957), using radioactive calcium and electrophoretic technics to study the binding of calcium to protein, showed that the parathyroid hormone increased the fraction of ionized calcium in the serum. The hormone mobilizes calcium and phosphate from bone. This occurs in nephrectomized rats and is therefore an extrarenal function of the hormone. It was shown by Bollet *et al.* (1963) that the parathyroid hormone, when administered to guinea pigs, caused a consistent significant decrease in femoral calcium concentration. There were no changes in collagen or polysaccharide. Thus, the hormone was shown to be capable of mobilizing mineral from bone without a concomitant decrease in concentration of matrix constituents.

It appears from the work of Neuman *et al.* (1956) that citrate plays an important role in the action of the hormone. They demonstrated that the parathyroid hormone produces a prompt increase in the arteriovenous difference in citrate levels in venous outflow from bone. Thus, the chelation of calcium by citric acid may be an important factor in the mobilization of calcium and phosphate from bone induced by the hormone.

Hiatt and Thompson (1957) showed that the intravenous administration of parathyroid hormone in normal man caused a phosphate diuresis, owing to a rise in filtered phosphate secondary to a rise in glomerular filtration rate, with no decrease in the tubule threshold for phosphate. In hypoparathyroid patients the hormone produced an accompanying decrease in tubular threshold for phosphate, as well as an increase in glomerular filtration rate. These changes in renal hemodynamics are effected in man by the acute intravenous injection of the hormone without producing hypercalcemia. However, the prolonged subcutaneous administration of the hormone produces hypercalcemia and a decrease in the renal tubular threshold for phosphate.

Rasmussen (1958) observed that the parathyroid hormone loses its activity upon oxidation with hydrogen peroxide. The reaction is reversible as shown by the restoration of activity by subsequent reduction with cysteine. The reversibility of the oxidation is dependent upon the pH of the medium. It is of interest to note that the mechanism of ACTH and the parathyroid hormone involves a triphosphopyridine-nucleotide oxidation-reduction system (Neuman and Neuman, 1958).

Grollman (1954) demonstrated that the hypocalcemia and tetany following parathyroidectomy in the dog could be effectively controlled by the intraperitoneal injection of an electrolyte solution having the composition of an ultrafiltrate of blood enriched with calcium. In the thyroparathyroidectomized dog with a nephrectomy, hypocalcemia and tetany occurred. The nephrectomized animal responded to parathyroid hormone injection. The response continued for some weeks if the animal was subjected to intermittent peritoneal lavage. Thus, it appears that the action of the parathyroid hormone is mediated mainly through the mobilization of osseous calcium and phosphate, and the changes in renal hemodynamics are secondary to this action.

Vincent *et al.* (1962) reported a case of abnormal behavior following parathyroidectomy. Seven other cases from the literature were reviewed. Electroencephalographic changes, which they believe may be related to changes in spinal fluid pressure and spinal fluid and serum calcium levels, were observed. The prompt administration of vitamin D caused a salutary reversal of these abnormalities.

Primary hyperparathyroidism is a comparatively rare disease. Kidney damage appears to be a constant finding if the hypercalcemia is not reduced. This condition may progress resulting in uremia and death. It is clear that in this condition parathyroidectomy is indicated (Hellström, 1962).

The chemical constitution of the parathyroid hormone has not been determined. Tweedy (1936) brought forth evidence to show that the principle responsible for the calcemic levels is, like insulin, in the nature of a protein. The active parathyroid hormone was separated by L'Heureux *et al.* (1947) into fractions of low and high molecular weight proteins. They observed that only the low molecular weight fraction elicited the hypercalcemic effect.

The secretion of the substance from the parathyroid glands appears to be under the control of the *anterior lobe of the pituitary.* Houssay (1936) demonstrated that pituitary insufficiency in the dog is associated with cellular atrophy of the parathyroid glands. The administration of ACTH causes the proliferation of the parathyroid structures and a rise in serum calcium.

**Clinical tetany.** In adults, tetany occurs most frequently as a result of surgical ablation of the parathyroid glands for various causes. The serum calcium drops to 7 or 8 mg. per cent. The striking symptoms are those resulting from nervous hyperexcitability. The hypertonic state of the muscles causes the feet and hands to be drawn into typical tonic contractions referred to as *carpo-pedal spasm.*

In infants the disease is generally associated with *calcium deficiencies, rickets, severe gastro-*

*intestinal disturbance*, and *alkalosis*. The spasms are much more generalized, and the syndrome is referred to as *spasmophilia*. The deficiency of calcium causes only the muscular twitchings. The frank convulsive state, on the other hand, results from the alkalosis. This in turn develops from the hyperpnea when muscular twitchings and calcium deficiency increase heat production. Bryan and Garrey (1931) showed that increasing the temperature precipitates a convulsion in a parathyroidectomized animal. Lowering the temperature was found to mitigate the seizures.

**Treatment of clinical tetany.** This condition is treated by elevating the serum-calcium level by the intravenous injection of calcium gluconate. As a rule, 1 gm. is administered. Simultaneously, parathyroid injection is administered. The parathyroid injection may be administered intravenously at first; usually 100 to 200 units are slowly injected. Subsequently 25 to 50 units of the injection are given every 6 to 12 hours intramuscularly until the crisis of the disease is over. Resistance to the effect of the parathyroid injection may occur with continued doses. A rich calcium diet is instituted, and vitamin D is also indicated. The parathyroid hormone *mobilizes calcium from the skeleton* but does not increase its absorption from the gut. If satisfactory results are not achieved with parathyroid injection or the patient becomes refractory to its effects, dihydrotachysterol may be given orally 0.625 to 6.25 mg. daily.

**Calcium Gluconate, U.S.P.** Calcium gluconate is the normal calcium salt of gluconic acid. It contains about 9 per cent of calcium. The compound is used as a convenient and *comparatively nontoxic* source of calcium. The compound is a white crystalline powder without odor or taste. It is soluble in 30 parts of water.

From time to time many different kinds of calcium salts have been used in therapy. These include calcium chloride, calcium lactate, calcium levulinate, and calcium arabonate. Calcium gluconate appears to be the salt of choice. The oral dose is 5 gm. 3 times daily. There appears to be little danger of over medication with calcium gluconate orally. However, this condition does not prevail when the salt is given intravenously. The intravenous dose is 0.2 to 1.0 gm.

The severe symptoms of hypercalcemia (20 to 25 mg. per cent) were mentioned on page 902. The intravenous injection of calcium salts may produce cardiac effects of a serious nature. The intravenous injection of calcium salts in man in a few instances has produced *bradycardia* and *death*. The danger is much more pronounced in the digitalized patient, page 649. Bedinger *et al.* (1942) produced ventricular fibrillation and cardiac arrest in normal and parathyroidectomized dogs by the intravenous injection of massive doses of calcium gluconate. Winkler *et al.* (1940) found that the series of cardiac events which occurred upon the intravenous administration of toxic amounts of calcium salts were as follows: (1) *vagal bradycardia*, (2) *ventricular arrhythmia*, and (3) *ventricular fibrillation*. Indeed, these toxic effects of large doses of calcium salts are not cited to suggest that calcium should never be given intravenously. It may be desirable to give the salt by this route for prompt effect in severe tetany. Nevertheless, the administration should be enjoined with adequate awareness of the potential hazard.

**Other uses of parathyroid hormone.** The effect of parathyroid hormone in the mobilization of calcium has been used in the treatment of *fluoride* and *oxalate poisoning*. These anions produce hypocalcemia.

**Dihydrotachysterol and calcium.** In the irradiation of ergosterol, various types of sterols are formed, page 900. In 1934 Holtz *et al.* obtained an active product which has had use in hypocalcemic states. This substance is *dihydrotachysterol, Hytakerol* or *A.T.10.* The primary effect of dihydrotachysterol is to *increase the absorption of calcium from the gut*. In this respect it acts like vitamin D. The urinary phosphate excretion is increased by dihydrotachysterol which causes a lowered serum phosphate and calcium mobilization. Obviously, this sterol therefore is of no value in rickets.

Dihydrotachysterol, like parathyroid hormone, is useful in states of hypocalcemia. It is effective orally and thus offers advantage over parathyroid hormone. It is said not to produce tolerance or refractoriness. Bernstein and Goldberger (1946) used dihydrotachysterol successfully in treating diffuse *scleroderma* caused by hypocalcemia as a consequence of parathyroid injury in subtotal thyroidectomy.

Dihydrotachysterol is supplied as an oil solution of the sterol. It is given in capsules 0.625 mg. per capsule, or in solution 1.25 mg./ml. The initial dose is 2.5 to 6.5 mg. daily for several days. Calcium salts should be freely administered orally. When the acute symptoms of the hypocalcemic state subside, 1.25 to 5.5 mg. once or twice weekly suffice for maintenance.

Overdosage with dihydrotachysterol will produce *hypercalcemia*, *anorexia*, *nausea*, *vomiting*, *headache*, *renal calculi*, and *stupor*. The symptoms disappear, as a rule, upon the withdrawal of the sterol.

The relative effectiveness of parathyroid hormone, dihydrotachysterol, and vitamin D on calcium absorption and phosphorus excretion is shown in table 56-1 from Albright and Reifenstein (1948).

In causing the reabsorption of calcium from bone, parathyroid hormone has the greatest activity of the 3 agents. Next is dihydrotachysterol, and third is vitamin D. The action of calcium reabsorption by dihydrotachysterol is delayed but of longer duration than that afforded by parathyroid hormone.

TABLE 56-1

*Calcium and Phosphorus Absorption and Excretion*

| Agent | Calcium Absorption | Urinary Phosphorus Excretion |
|---|---|---|
| Parathyroid hormone...... | + | ++++ |
| Dihydrotachysterol........ | ++ | +++ |
| Vitamin D................. | ++++ | ++ |

THE ROLE OF PHOSPHATES

All of the forms of phosphorus found in the living organism are either esters or salts of the tribasic ortho phosphoric acid $H_3PO_4$. Of the approximately 700 gm. of phosphorus present in the human body, about 600 gm. is present in the bones, mainly as the phosphates of calcium. Orthophosphoric acid dissociates according to the following equations.

$$H_3PO_4 \rightleftarrows H^+ + H_2PO_4^-$$

$$H_2PO_4^- \rightleftarrows H^+ + HPO_4^{=}$$

$$HPO_4^{=} \rightleftarrows H^+ + PO_4^{\equiv}$$

The 3 dissociation constants of phosphoric acid are of such degrees of magnitude that at pH 7.4, 82 per cent of the total inorganic phosphate of the plasma is in the form of the divalent ion $HPO_4^{=}$. About 18 per cent is present as the univalent ion $H_2PO_4^-$, and inappreciable amounts are there as the trivalent ion $PO_4^{\equiv}$. The buffer action of this phosphate system is an important component of the buffer capacity of the plasma.

Phosphoric acid enters into ester formation with lipids and proteins. These combinations play important roles in the metabolism of complex enzyme systems. Lecithin and sphingomyelin are phosphorized fats. Phosphoric acid forms many very labile esters which are associated with the utilization of carbohydrate and muscle contraction, such as hexose phosphates and adenosine triphosphate, page 857. These esters of phosphoric acid contain energy-rich phosphate bonds which supply immediate energy for muscle contraction. The tissue cells are apparently capable of synthesizing all of the complex esters of phosphoric acid from inorganic phosphate. For example, the human organism is incapable of thiamine synthesis. Nevertheless, if thiamine is supplied the tissues can readily convert it into its active form *diphosphothiamine*, known as *cocarboxylase*. Actually, thiamine must undergo phosphorylation before it is able to exert its biologic activity in the body.

**Requirements and absorption of phosphorus.** Like calcium, phosphorus is a *ubiquitous* element. Its presence in the soil carries it into plant tissues and hence to animal cells as well. In the ordinary diet of vegetable and animal constituents there is a constant flow of phosphorus compounds into the alimentary tract. It is estimated that the average daily requirement for man is about 1 gm. It may, however, be higher in growing children where bone formation is in active progress.

Although most phosphorus compounds are readily absorbed from the gastrointestinal tract, a considerable proportion of ingested phosphorus occurs in the stools (McLean, 1942). This, however, does not indicate that all of this phosphorus was not absorbed. Much of this phosphorus is likely excreted into the gastrointestinal tract in the form of enzymes. "It is thus conceivable that the same phosphate ion might be released into the gastrointestinal tract and reabsorbed a dozen times before being finally ejected with the excreta" (McLean, 1942).

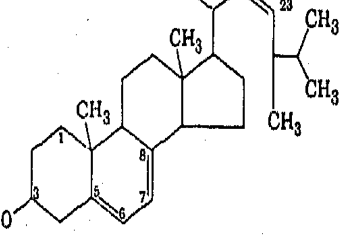
The phosphate which is determined in the blood is inorganic phosphate. It is usually reported as elementary phosphorus. In infants the inorganic phosphorus ranges from 4.5 to 6 mg./100 ml. of serum. Adults, as a rule, show a lesser quantity; the norm ranges from 3 to 4 mg. per cent.

**Phosphorus deprivation.** When phosphorus is withdrawn from the diet or deficiency is produced by other causes such as vitamin D deficiency, the *bones fail to calcify*. The *rarefaction* of the *skeleton occurs*, and *death* follows. In phosphorus-deficient rats the bones become soft and pliable, and one of the common symptoms is the collapse of the thoracic cage owing to the softness of the ribs. Day and McCollum (1939) demonstrated that in rats on a phosphorus-deficient diet the soft tissues held most tenaciously to their phosphate, and the element was supplied by the skeleton.

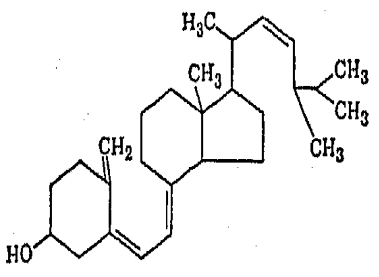
The control of phosphorus as well as calcium metabolism is dependent upon the presence of adequate supplies of vitamin D.

**Vitamin D.** The existence of vitamin D as an entity separated from and independent of vitamin A was shown first by McCollum *et al.* in 1922. In 1925 Hess and Weinstock irradiated pieces of human skin; this was fed to rats and found to possess antirachitic properties. In 1927 Windaus showed that the substance capable of developing antirachitic properties was ergosterol, a sterol found in ergot. This substance which was activated by the irradiation of the skin was likely a related sterol.

Through the chemical investigations of Windaus and Thiele (1935) the structure of vitamin D has been established. The structures of ergosterol and vitamin $D_2$ (calciferol) are shown in the accompanying formulas.



Ergosterol

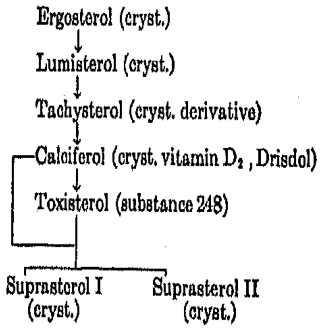


Calciferol or Vitamin $D_2$

It will be observed that calciferol is formed from ergosterol through the rupture of the $C_9—C_{10}$ carbon linkage.

Eventually it was found that 7-dehydrocholesterol was the principal sterol of natural origin which gave rise to the antirachitic substance called vitamin $D_3$. Vitamin $D_3$ differs from calciferol in its chemical constitution in that it contains a saturated carbon chain with 1 less carbon atom attached to the 5-carbon ring.

The following substances are formed by the irradiation of ergosterol:



Ergosterol (cryst.)
Lumisterol (cryst.)
Tachysterol (cryst. derivative)
Calciferol (cryst. vitamin D2, Drisdol)
Toxisterol (substance 248)
Suprasterol I (cryst.)
Suprasterol II (cryst.)

It was determined that vitamins $D_2$ and $D_3$ each showed about 40,000 U.S.P. units of vitamin D activity per milligram by the rat assay method. When tested in the chick, however, about 100 times the number of units of vitamin $D_2$ as of $D_3$ are required to produce equal bone ash assays. In man this difference in potency does not prevail. Vitamins $D_2$ and $D_3$ have been equally efficacious in the treatment of rickets (Gerstenberger *et al.*, 1940). Crystalline calciferol (vitamin $D_2$) was the former standard of comparison for medicaments containing vitamin D. One milligram of calciferol represented 40,000 units of antirachitic activity. In conformity with the action of the World Health Organization of the United Nations, the U.S.P. has adopted 7-dehydrocholesterol as the standard of comparison. This substance is vitamin $D_3$, and 1 mg. of the crystalline standard elicits the antirachitic activity of 40,000 U.S.P. units of vitamin D.

**Vitamin D assays.** A vitamin D deficiency can readily be produced in white rats by the feeding of a *vitamin D deficient-diet* in addition to an *unfavorable Ca/P ratio.* The most significant feature of this diet is the rapidity with which the symptoms of *rickets* develop. The most striking feature of the rachitic bones is their low calcium and phosphorus content; the proportion of inorganic to organic matter is greatly diminished. The relationship between the calcium and phosphorus content seems, however, to be the same as in normal bone.

When rachitic rats are fed cod liver oil or other substances rich in vitamin D the rachitic condition rapidly disappears, and the bone returns to

normal. Use is made of this test in detecting the presence of vitamin D in foods and medicines which contain it. Further, it may be employed to assay quantitatively the vitamin content of various products. The precise methods for the biologic assay of products containing vitamin D are given by the United States Pharmacopeia.

There are also chemical methods of assaying vitamin D. Wilkie *et al.* (1958) developed a most satisfactory method for the determination of vitamin D. The method involves chromatography and color inhibition. The procedure appears to be reliable and most valuable for the detection of vitamin D deterioration, that so readily occurs in preparations containing the vitamin and calcium salts (Nelson, 1959).

**Rickets.** This disease has been recognized for centuries. Homer in the Iliad in 950 B.C. described the symptoms of rickets. Medieval pictures of the Madonna with the Christ child showed the infant to have the *bowed legs* and *pot belly* characteristic of the disease. The malady appears to be primarily associated with a calcium-phosphorus and vitamin D deficiency. The simplest conception of the disease entity is that the symptoms and findings are due to a *diminished plasma phosphate level*.

Rickets is a childhood disease, and in it the lowered phosphate level of the plasma prevents the ossification of the skeleton; hence, the osseous deformities. While there is abundant experimental and clinical evidence that calciferol will obliterate the symptoms of the disease, the underlying pathology and exact mechanism of action of calciferol still remain obscure.

In rickets there is an increased excretion of calcium and phosphorus in the urine. Invariably the phosphates of the plasma are diminished. Simultaneously there occurs an increase of the enzyme *phosphatase* in the blood. The function of this enzyme appears to be to hydrolyze phosphoric acid esters into ionizable inorganic phosphate. Actually the *rise of plasma phosphatase* has become *diagnostic* in the detection of *rickets.* Phosphatase originates in the osteoblastic cells and is abundant where bones are actively forming. It has been suggested that one of the fundamental lesions in rickets is the loss of phosphatase from the bones. Here its function is to de-esterify phosphoric acid esters and make available inorganic phosphate to combine with calcium to lay down the osseous structure. Studies *in vitro* demonstrated that a water-soluble phosphorylated vitamin $D_2$ activates the alkaline phosphatase of kidney, intestine, and particularly of bone. Definite proof of this hypothesis has not been established; nevertheless, the concept appears to possess merit.

**Vitamin D and phosphorus metabolism.** The principal action of vitamin D is to increase the *inorganic phosphates of the blood.* It affects also calcium metabolism and causes tricalcium phosphate to be laid down in the skeleton. Harrison and Harrison (1941) have demonstrated that vitamin D promotes the reabsorption of phosphate by the renal tubules. Through this mechanism the plasma phosphate level is elevated. The excessive excretion of phosphate is one of the primary disturbances in rickets.

For many years increasing the absorption of phosphorus from the gut was considered one of the principal actions of vitamin D in the cure of rickets. Morgareidge and Manly (1939), using radioactive phosphorus, demonstrated that the principal action of vitamin D was not to increase the absorption of phosphorus from the gut but to increase the phosphorus content of the bones. It has been suggested also that the action of the vitamin is primarily on the *bone cells* and *not on the intestinal absorption of phosphorus.*

It has been established that the citrate content of bone is low in rickets. Carlsson *et al.* (1954) showed that an increased citrate content of bone is one of the initial signs of improvement with vitamin D therapy. Since citrate is not formed in sufficient quantity by parathyroid hormone alone, Neuman and Neuman (1958) suggest that both the hormone and vitamin D are essential for adequate citrate levels in bone. It is further suggested that it is achieved by the 2 agents by blockading the oxidative cycles of carbohydrate metabolism at different sites. The problem of why parathyroid hormone alone causes decalcification of bone, and vitamin D evokes the calcification process, remains unanswered. However, the formation of citrate in bone by each agent seems to be a useful clue.

Parathyroid hormone and vitamin D produce hypercalcemia. The action of the former, as has been stated, is at the expense of the skeleton. Indeed, parathyroid hyperplasia accompanies avitaminosis D as a compensatory mechanism. Vitamin D increases the amount of calcium absorbed from the gut and simultaneously diminishes its urinary excretion. Consequently, the spasmophilia which is often associated with rickets, owing to hypocalcemia, is cured by the administration of vitamin D. It is clear that vitamin D and the parathyroid hormone are different substances eliciting different actions at different sites. However, the two responses are synergistic, and their common action is to elevate the serum levels of the calcium and phosphate ions.

The average curative dose of vitamin D in rickets is about 5000 units daily. The administration of the vitamin should be accompanied always by adequate calcium and phosphorus intakes in the daily diet. Exposure to sunshine is also helpful. The prophylactic dose in infants is from 400 to 800 units daily.

**Other uses of vitamin D.** The administration of vitamin D has been found to be useful in the treatment of *osteomalacia* in adults.

In periods of increased demand for calcium and phosphorus such as during *pregnancy* and *lactation*, vitamin D is useful in increasing the availability of the dietary phosphorus and calcium to meet the excessive demands of the organism.

The healing of fractures was claimed to be accelerated by using vitamin D, parathyroid hormone, and calcium and phosphorus therapy (Nelson and Nelson, 1941).

**Symptoms of overdosage with vitamin D.** The early symptoms of vitamin D intoxication are *nausea*, *anorexia*, *headache*, *polyuria*, *lassitude*, and *diarrhea*. Calcium deposits may be produced in the kidney and in the lumen of the arteries. Kidney function may also be impaired. Freedman (1957) observed one individual who developed renal colic from an overdosage of the vitamin. Hypercalcemia was present 15 months after the withdrawal of vitamin D. The increased hypercalcemia increases the viscosity of the blood and may induce circulatory collapse.

Scholz and Keating (1955) pointed out that a significant factor in the diagnosis of vitamin D intoxication is the presence of hypercalcemia and the absence of hypercalciuria. Further rapid improvement generally ensues with the withdrawal of milk and alkali from the diet.

Idiopathic hypercalcemia appears to be associated with the ingestion of excessive amounts of vitamin D. A reduction of the level of vitamin D intake decreased the incidence of the disease in a controlled study in infants in Great Britain and the United States. There appears also to be a hypersensitivity to vitamin D present in infants associated with the pathogenesis of the disease. It is of interest to note that Fellers and Schwartz (through Fraser 1961) identified a substance with vitamin D activity in the serums of 3 patients suffering with severe hypercalcemia. These investigators consider hypercalcemia a disease resulting from an inborn error of metabolism.

Steck and his associates (1937) observed that dogs, as a rule, were able to survive 22,000 units of calciferol/kg. for indefinite time periods. For the average dog of 10 kg. this means 220,000 units. In 700 cases of human subjects who received 100,000 units daily, less than 10 per cent showed any toxic manifestations. The symptoms disappeared upon the cessation of therapy. Deaths have resulted from the administration of 20,000 to 40,000 units daily for several months. However, rachitic children will readily tolerate 200,000 to 300,000 units daily.

Bauer and Freyberg (1946) emphasize the danger of renal damage owing to massive doses of the vitamin. Contamination of calciferol with toxisterol appears to be a possible hazard. However, within very wide margins the vitamin appears to be devoid of toxic action in its rational therapeutic uses.

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# 57

# *Neoplastic Tissue Metabolism: the Chemotherapy of Cancer*

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In chapter 45, concerned with the response of hematopoetic system to drugs, consideration was given to the use of chemotherapeutic agents in the treatment of leukemia. This disease may be considered as a neoplastic disease in which the proliferation of cells manifests itself in the blood stream as a plethora of various types of immature leukocytes. Definitive strides have been made in the treatment of this disease. The consideration in this chapter will be the chemotherapeutic approach to the control of growth of solid tumors of various organs and to the suppression of metastases.

Since the end of World War II there has been a complete revolution in the attitude of the public and scientists with respect to chemotherapy of cancer. Hope and an active, positive research program on many fronts have replaced despair and a paucity of investigations in this field. The new research programs are multi-disciplined and receive adequate support from public and private funds. In general, the broad programs of basic research in the cancer field have as their aims the following goals:

1. The determination of the differences between the metabolic processes of normal and neoplastic tissue
2. The determination of the mechanism of the host factors against the invasion of neoplastic growth
3. The elucidation at a cellular and enzyme level of the mechanism of action of growth-

ARNOLD M. SELIGMAN

*Outstanding American Investigator in Cancer Chemotherapy*

"It appears that the greatest success with alkylating agents in the treatment of cancer will be achieved, either when the drug deleteriously affects the tumor cells by virtue of their enzymatic peculiarity, or when the drug can be brought to the tumor cells without reaching a significant portion of the bone marrow."

inhibiting and anti-cancer agents including the antimetabolites and hormones

4. A more definitive description of the natural history of cancer in man
5. Basic investigation of the genetics and etiology of cancer

This broad approach to the problem of cancer in such institutions as the National Cancer Institute of the National Institutes of Health and the Sloan-Kettering Institute for Cancer Research and the University Laboratories throughout the world has shown significant progress. Further delineation of the metabolic differences between normal and cancer cells has been made. Useful drugs have been developed for use in palliating certain types of cancer, and, further, an awakening of public and scientific interest in the field has been salutory.

**Normal and neoplastic tissues.** Neoplastic tissues are composed of cells that are autonomous and often, although not always, grow rapidly. Cancer cells grow and invade inexorably. They either grow or die, although they may infrequently lie dormant for many years. Warburg's observation of a generation ago has been confirmed repeatedly; namely, that tumors are characteristically and distinctly glycolytic in their metabolic processes. This is in contradistinction to normal tissue in which the main line oxidation process preponderates, and glycolysis provides the lesser amounts of energy in the metabolic process. In tissue culture studies normal cells become more strongly glycolytic, but the respiratory process still exceeds the process of glycolysis. Warburg stated regarding this phenomenon, "When we say that normal cells only breathe and do not ferment, we must qualify this statement by adding that normal cells must have been grown in the body." The distinction between glycolysis and respiration in normal and cancer cells is more marked when the tissue measurements are made *in vivo* (Graff, 1959).

Greenstein (1954) showed that tumors of widely different etiologies and histogenesis have a nearly uniform pattern of metabolism. No matter from which normal tissue the tumors originate, their metabolic patterns resemble each other more closely than do those of normal tissues. The enzyme distribution and activity in all tumors are strikingly similar. Normal tissues have different functional activities, but in tumor tissue the predominating functions are *growth* and *invasion*.

Graff (1959), from tissue culture studies on normal and tumor cells, made certain cogent observations regarding the behavior of the tissues with respect to the TCA cycle. He stated, "Cancers unlike normal cells, behave alike, both inside and outside the body." He considers that cancer cells result from a mutational process, which gives rise to cells that do not have the capacity to mature or differentiate completely in response to host regulatory mechanisms. Their fixed immaturity causes them to exhibit functional aberration. Their dependence upon glycolysis is likely to be sequential to their incapacity to respond adequately to the regulatory mechanisms of the host. In any case, their most malignant property is autonomy.

Since the tumor cell can exploit biochemical differences between normal and tumor cells to maintain itself at the expense of the host, encouragement is given investigators to exploit the differences between normal and malignant cells as a basis for selective antitumor toxicity of externally administered agents. To do this effectively knowledge of the cell must be much more complete than it is at the present time. Some recent attempts to evolve agents on the basis of quantitative differences in enzyme activity will be discussed later.

## IONIZING RADIATIONS

The fundamental particles which compose the structure of atoms are the proton, neutron, and electron. The atoms of most elements are stable and do not emit emanations. In 1896 Becquerel discovered that certain ores containing uranium are continuously emanating ionizing radiations. The emanation was found to consist of 3 distinct types of rays; namely, positively charged *alpha rays*, helium nuclei, *beta rays*, which are fast moving electrons, and *gamma rays*, which are electromagnetic waves of short wave length equivalent to x-rays. The 3 types of atomic emanation are *ionizing radiations*, *i.e.*, they are capable of converting the atoms of various compounds into ions on impact. Since gamma radiation is the equivalent of x-ray, it would follow that this property is also shared by x-ray radiation.

The profound biologic effects of radium emanation and x-ray have been recognized for more than a half-century. Although these effects are mainly on the bone marrow, all tissues may be deleteriously affected depending upon the intensity and duration of exposure. Especially susceptible are tissues whose cells are undergoing rapid mitotic activity such as intestinal epithelium as well as bone marrow. It is clear that since ionization radiations are capable of initiating chemical changes in the medium through which they pass they are therefore capable of evoking profound changes in living tissues. These changes may result in (1) the instant death of the cell, (2) injury inhibiting mitotic division, (3) depression of cellular functional activity, and (4) mutational changes in germ cells. Since life processes take place in water and an abundance of water molecules exists in all living cells, probably the most significant biologic effect of ionizing radiations stems from their action on the molecules of water.

**Effect of ionizing radiations on cells.** The effect of ionizing radiations on water is primarily one of cleaving the water molecule into hydrogen and free hydroxyl radicals as well as the ions. These uncharged particles are chemically very reactive and can serve as oxidizing and reducing agents. They are capable of cleaving the carbon-to-carbon atom bond. Furthermore, the interaction of 2 hydroxyl radicals may give rise to the production of hydrogen peroxide, which can produce biologic changes within the cell. This is why the regional intra-arterial injection of hydrogen peroxide enhances the effects of x-ray radiation. Sulfhydryl groups of enzymes may be inactivated by oxidation to the disulfide form (Barron, 1954). Amino acids may be deaminated to form ammonia, and hydrogen sulfide may be formed from cysteine by ionizing radiations. The formation of hydrogen sulfide and ammonia within the cell may be detrimental to its vital processes (Dale, 1954). This also explains why sulfhydryl rich compounds such as cysteine or BAL protect animals from radiation damage when large doses are injected intravenously prior to exposure.

Thus, it is clear that by direct action or through the ionization of water, radiations can produce the profound changes in cellular constituents. The effects of ionizing radiations extend to the cellular nucleic acids. Hevesy (1949) showed that x-rays caused a decrease in the uptake of $C^{14}$ into desoxyribonucleic acid. Butler (1949) demonstrated that x-rays caused a depolymerization of nucleic acids. It was suggested that the viscosity change initiated by radiation is possibly a self-propagating colloidal phenomenon. It is well known that exposure of normal tissue to ionizing radiations can so affect the cells that malignant transformation will result. The latent period for this effect in the skin of man is about 20 years.

From these studies it is clear that ionizing radiation can modify the chemical structure of cellular constituents, inactivate enzymes, alter the metabolic pattern, and produce changes varying in range from intensified function to complete destruction. It may alter the host-tumor relationship in either direction.

These actions are unique from a pharmacologic standpoint, as they are initiated by a physical process and not by the intervention of a single, known chemical compound.

**Basis for the use of ionizing radiations in cancer.** Living cells appear to be more readily injured by ionizing radiations during their mitotic cycle. In many cancers mitotic cell division occurs at a rapid rate, and, therefore, the tumor tissue is more sensitive to radiation than the normal adjacent tissue. Tumors vary greatly in their sensitivity to radiation and the degree of radiation applied is usually that required to suppress tumor growth. The degree of radiation required to destroy completely most tumors would exert a marked deleterious effect upon the surrounding normal tissue. The danger of overexposure is a limiting factor in radiation therapy. Radiation therapy (x-ray) can be effectively used in retarding the growth of localized, nonresectable cancer and suppressing symptoms. If the disease has undergone metastases, it is possible only to relieve the most distressing symptoms by regional exposure to x-ray therapy, such as x-ray therapy of metastases to a spinal vertebra.

Because of the limiting factor of profound tissue damage by x-ray therapy, radiation emanating from naturally-occurring radioactive elements such as radium, and artificially prepared radioactive elements such as radioactive iodine, phosphorus, or cobalt have found a definitive place in the treatment of leukemia and certain types of cancer. In limited cases they appear to provide a definite therapeutic advantage over x-ray therapy.

**Radium.** The element radium, which has an atomic weight of 226.1 and an atomic number of 88, is composed of 4 isotopes. The most abundant isotope is $Ra^{226}$ and is the isotope generally used in medicine. It emits alpha and gamma rays and has a half-life period of 1600 years. Radium in the form of its chloride salt may be considered as a source of high energy electromagnetic waves (gamma rays) similar to those produced by high voltage x-ray equipment. The relative penetrating power of alpha and beta particles and gamma rays approximately is in the order of 1 to 100 and 10,000. Therefore, the alpha and beta particles can be readily removed by a thin metal or plastic filter to yield pure gamma radiation and thus avoid the major damaging effects on skin of the larger particles. Dosage is measured in units called "curies." A curie is defined as the amount of radioactive substance which decays at the rate of $3.7 \times 10^{10}$ disintegrations per second. For medical purposes the millicurie, mc. ($1/_{1000}$) and the microcurie, µc. ($1/_{10^6}$) are employed.

After the elimination of an alpha particle from the nucleus of a radium atom, radium is converted into another element, *radon*, which is a radioactive, noble gas. Radon is continuously emanated from slightly acidified solutions of radium salts. The gas may be removed from the mother element radium, purified, liquefied, and sealed in capillary tubes. These tubes may be applied to or implanted in tumor tissue and they produce essentially the same effects as radium. Radon has the advantage of a short half-life period of 3.8 days; it decays through emission of an alpha particle into polonium$^{218}$ and, therefore, must be prepared from the radium source at frequent intervals. Since the development of synthetic radioactive isotopes such as cobalt$^{60}$, the use of radium and its emanation in the treatment of cancer appears to be diminishing.

### Artificial Radioactive Isotopes

When a neutron is shot into the nucleus of a stable atom of an element, the nucleus may be so altered that the element becomes radioactive. For example, the phosphorus atom contains in its nucleus 15 protons and 16 neutrons. Thus the phosphorus atom has a mass of 31. By bombardment of the nucleus of $P^{31}$ with a high speed charged particle like the ion of heavy hydrogen or deuteron, the proton with a positive charge will be repelled, but the uncharged neutron will enter the nucleus of the phosphorus atom. The atom now has 17 neutrons and is $P^{32}$; this nucleus is unstable and $P^{32}$ is radioactive.

The success in therapy with an artificially prepared radioactive isotope is dependent upon many factors. First, the radioactive atom must enjoy a high tissue uptake by the organ to be treated. Second, there must be a high rate of turnover of the exchangeable radioactive atom in the tissue. Third, the half-life of the isotope or its sojourn in the body must be sufficiently short so that a therapeutic dose can be delivered within a reasonably short time so that normal tissue is not deleteriously affected by the emanation from the circulating isotope. *Radioactive phosphorus*, page 734, meets these criteria to a great extent and has been used successfully in the treatment of leukemia and polycythemia vera.

**Radioactive Iodine, $I^{131}$.** Radioactive iodine has been discussed previously under the heading of iodine metabolism, page 885. It is employed extensively for the measurement of the avidity of the thyroid gland for iodine and also in the treatment of hyperthyroidism.

Radioactive iodine is one of the fission products of uranium. Since the isotope is volatile like ordinary iodine $I^{127}$, it may be readily separated and purified by distillation. $I^{131}$ is also prepared from tellurium by bombardment with slow neutrons in a chain-reacting pile. Radioactive iodine in its elementary state or in salt form such as sodium iodide decays with the emission of 2 beta particles (of 0.315 and 0.6 million electron volts of energy, respectively) and 4 gamma rays (of 0.638, 0.636, 0.283 and 0.08 million electron volts of energy, respectively). Its half-life period is 8 days.

The success of radioactive iodine in the measurement of thyroid activity and the treatment of hyperthyroidism has not been paralleled in the treatment of carcinoma of the thyroid gland. Unfortunately, the uptake of $I^{131}$ by the neoplasm is generally low and the uptake of the isotope is confined principally to that portion of the gland which is not involved in the disease process.

A general treatment procedure for metastatic carcinoma of the thyroid gland was outlined by Beierwaltes *et al.* (1957). The patient is checked to make sure that total thyroidectomy has been performed. The maximal uptake of $I^{131}$ by the metatases is determined. The patient is hospitalized and given the treatment dose of $I^{131}$. The urinary excretion of the isotope is followed, and when the body content of $I^{131}$ has dropped to less than 30 mc., the patient may be dismissed from the hospital according to the requirements of the Atomic Energy Commission Standards. No further medication is given and the patient is hospitalized again in 3 months. Chest stereoroentgenogram, BMR, serum cholesterol, PBI, and $I^{131}$ tracer studies are performed to determine if any residual metastases are present. If these are found, another dose of $I^{131}$ is administered. This program of study is continued until the patient becomes myxedematous and there is no further $I^{131}$ uptake by the metastatic growth. Thyroid powder is administered in sufficient dosage to render the patient euthyroid. The follow-up of the patient is continued every 6 months with the foregoing procedures, withholding the thyroid medication for a period of 6 weeks before the diagnostic studies.

Individual doses of $I^{131}$ in thyroid cancer range from 1 to 100 mc. A total dosage of several hundred millicuries is often required. Pregnancy after the first trimester is a contraindication in $I^{131}$ therapy because $I^{131}$ passes through the placenta and may destroy the fetal thyroid gland to produce a cretin. Lactating mothers excrete the isotope in the milk and it is hazardous to the infant's thyroid gland. This complicates urinary excretion studies.

$I^{131}$-labeled serum albumin is used in liver scanning to visualize liver metastases. The albumin is rapidly taken up by the normal liver cells and when $Au^{198}$ or Thorodrast is used the Kupfer cells take up the radioactive isotope. This leaves negative shadows of metastatic carcinoma on the scan, which is done with highly directional scintillating counting equipment.

$I^{131}$ is official in the U.S.P. under the name of *Sodium Radio-iodide Solution.* Specific directions for handling and storage of the solution are given in the monograph.

**Radioactive Cobalt, $Co^{60}$.** Teletherapy units employ $Co^{60}$ as a reasonably inexpensive source of gamma radiation. It is estimated that $Co^{60}$ rods costing approximately $10,000 yield the radiation equivalent of $25,000,000 worth of radium. $Co^{60}$ has a half-life of 5.3 years and emits beta particles equivalent to 0.31 million electron volts and gamma rays equivalent to 1.17 and 1.33 million electron volts. Because of its shorter wave length, the radiation from $Co^{60}$ appears to be tolerated better by the skin than x-ray or radium emanation. The teletherapy unit with $Co^{60}$ provides a more precise tumor dosage, better depth dose and less skin and bone absorption. It appears to have special advantage for the treatment of carcinoma of the esophagus and bronchi and radio-resistant carcinoma of the cervix.

Radioactive cobalt salts have been used for irradiation of the bladder for the suppression of tumor growth. The solution containing the $Co^{60}$ salt is placed in flexible balloons and inserted in the bladder.

Vitamin $B_{12}$, $Co^{60}$-labeled, is used in the diagnosis of pernicious anemia.

**Radioactive Gold, $Au^{198}$.** Radioactive gold, $Au^{198}$, has a half-life period of 2.7 days. It emits beta emanation with energy equivalent to 0.96 million electron volts and gamma radiation equivalent to 0.411 million electron volts. $Au^{198}$ is used in the form of a colloidal dispersion of the element. It may be injected directly into tumor tissue and remains at the site of injection for considerable time periods, producing local radiation during its period of decay. The quantity of elementary gold is too small to produce toxic reactions characteristic of gold.

The most prevalent use of $Au^{198}$ is in the treatment of pleural and peritoneal effusions produced by cancerous involvement of these surfaces. It is most helpful in patients who do not have large masses of neoplastic tissue. The gold solution is infused into the pleural or peritoneal cavity. Usually initial doses of 125 mc. are used for the pleural cavity and 160 mc. in the peritoneum. When the $Au^{198}$ has decayed to the point at which the patient contains less than 30 mc. of radioactivity, he may be dismissed from the hospital.

Beierwaltes *et al.* (1957) consider that approximately one-third of the patients selected for the intercavitary treatment with $Au^{198}$ are benefited. The most promising results are obtained with ascites resulting from carcinoma of the ovary. The recurrence of fluid accumulation in either the pleural or peritoneal cavity may necessitate a further treatment with intercavitary $Au^{198}$.

Another agent that is used in the suppression of pleural and peritoneal fluid accumulation owing to metastatic growth is *Chromic radio-phosphate* ($CrP^{32}O_4$). The preparation is a colloidal suspension suitable for parenteral administration. The average specific activity of chromic radio-phosphate is 3 to 6 mc./mg., and the activity of the suspension is usually 2 to 3 mc./ml. $P^{32}$ is a pure beta emitter with a half-life of 14.3 days.

The usual dose of chromic radio-phosphate is 5 mc. intrapleurally and 10 mc. intraperitoneally. When necessary, doses may be repeated after an interval of several weeks.

## Hormonal Therapy

Gutman and Gutman (1938) observed an increase of acid phosphatase in the serum of patients with metastatic carcinoma of the prostate gland. It occurred to certain investigators (Huggins, 1943) that the rate of tumor growth might be retarded by depressing the androgen level of the serum. Accordingly, orchiectomy was performed on patients with prostatic cancer with a considerable degree of success in retarding the rate of tumor metastatic growth. Because the adrenal cortex is also a source of androgens, Huggins (1943) has performed adrenalectomy on such patients after orchiectomy.

It appears that although the growth of metastatic prostate cancer is favored by androgens, it is retarded by estrogens. In this condition estrogen therapy is used as a substitute for orchiectomy and after the surgical procedure. Their mechanism of action is not known, but evidence is convincing that they produce a mitigation of the local discomfort and retard the metastatic process. The beneficial effects may continue for months or even a few years. After a time it appears that the retardation of growth elicited by the estrogens ceases, perhaps because of an adaptation of the neoplastic growth to their action and to the increased autonomy that most cancers acquire with time.

Although most of the estrogenic compounds are effective in prostatic cancer, diethylstilbestrol is one that is extensively used. The recommended dose is 3 mg. daily intramuscularly or orally for several weeks. Then the dose is reduced to 1 mg. daily or 0.5 mg. 3 times daily orally. The principal side effect of estrogenic therapy is feminization.

Some of the estrogenic compounds, mainly diethylstilbestrol, ethinyl estradiol, dimestrol, estradiol dipropionate, and conjugated estrogenic substances, have been shown to be beneficial in certain cases of breast cancer. Generally, the palliative effect is seen only in those women who are at least 5 years beyond the menopause. The beneficial effect is not dependable, and estrogens are not recommended as primary treatment in mammary cancer if surgery and roentgen therapy are available to the case.

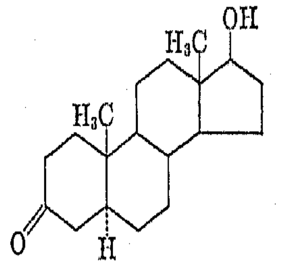
Landau *et al.* (1962) used a combination of 5 mg. of estradiol benzoate and 50 mg. of progesterone intramuscularly in the treatment of advanced breast cancer. Sufficient clinical improvement occurred in 9 of 15 patients to warrant the further investigation of this combination of hormonal therapy.

The preferred hormonal therapy for metastatic breast cancer is with androgenic compounds. It has been shown that they often produce symptomatic beneficial effects such as alleviation of pain, restoration of appetite, and weight gain. The beneficial effect of the androgens may be due partially to their anabolic activity.

Objective improvement of the patient occurs in a limited number of cases only. Metastatic soft tissue lesions at various sites may respond to treatment, but lesions in the central nervous system seldom respond to androgen therapy.

Testosterone propionate is one of the androgens used in breast cancer. The dosage schedule is 150 to 300 mg. intramuscularly weekly in 3 divided doses. The duration of therapy is usually 2 months for subjective response and generally 5 months before objective response is observed. Similarly Halotestin is used in daily doses of 6 to 20 mg. orally. The preferred dose of Halotestin is 10 to 20 mg. daily for 3 months.

**Stanolone (Neodrol)** is another androgenic compound which is used principally for its tumor suppressing action. Its structure is shown in the formula:



Neodrol (Stanolone)
Androstan-17 (β)-ol-3-one

Neodrol is a white crystalline powder which is insoluble in water.

Neodrol elicits the same type of virilization as does testosterone. Its principal use is mainly for its anabolic action and tumor-suppressing activity. The use is confined mainly to inoperable carcinoma of the breast and postoperative metastatic carcinoma of the breast.

Neodrol is administered by intramuscular injection of an aqueous suspension of the microcrystalline powder. The average effective dose is 100 mg. daily. This schedule of dosage is continued as long as it is accompanied by a clinical improvement of the patient and the untoward side effects of virilization and anabolic action can be tolerated.

**Dromostanolone Propionate (Droblan).** Droblan is another androstan derivative similar in action to Neodrol. Chemically, Droblan is 17β-hydroxy-2α-methyl-5α-androstan-3-one propionate.

Droblan evokes about 25 per cent of the activity of testosterone or methyl testosterone in suppressing pituitary gonadotropins in parabiotic rats. The drug provokes a reversal of negative balances for nitrogen, calcium, potassium, and phosphorus which is characteristic of physiologically active androgens.

Like Neodrol, Droblan is indicated in the treatment of advanced metastatic carcinoma of the breast. Droblan is administered intramuscularly, 100 mg. 3 times weekly. Treatment should be continued as long as satisfactory results are achieved. It appears that 6 to 8 weeks are required before the effectiveness of the treatment can be assessed. The side effects of Droblan are similar to those evoked by testosterone propionate, but are significantly less intense.

Cancers other than prostate and breast are not suppressed by estrogen or androgen therapy.

**Adrenocortical steroids.** The adrenocortical steroids are capable of causing a dissolution of lymphocytes, regression of lymphatic tissue, and growth retardation in certain mesenchymal tissues. Specific injury to certain cell types appears to be the basis for their chemotherapeutic activity in cancer (Karnofsky, 1958). In addition, the anti-inflammatory activity of the adrenocortical steroids is likely a factor in their beneficial effect in cancer. The adrenocortical steroids are especially efficacious in conjunction with other forms of therapy. This is notably true in leukemia, page 739, with anti-folic acid and 6-mercaptopurine therapy. Prednisolone has been widely used, but the newer adrenocortical steroids appear to be equally efficacious.

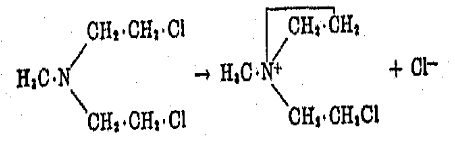
## Cytotoxic Agents

The cytotoxic agents are characterized by containing at least one and usually 2 or more reactive groups in the molecule and are capable of introducing alkyl groups into molecules that perform important cellular functions. They are often referred to as *polyfunctional alkylating agents.* Effective cytotoxic agents are injurious to rapidly proliferating cells such as are present in many tumors. They react with avidity with many cellular constituent molecules, especially carboxyl groups, sulfhydryl groups of protein, and phosphoric ester groups of nucleic acid. It is thought, moreover, that desoxyribonucleic acid (DNA), the genetic substance in the nucleus, is one of the main target molecules and is very vulnerable to their action. Unfortunately, the cytotoxic effect is not specific for neoplastic tissue, and the use of these agents is qualitatively similar to the effect of total body radiation. Bone marrow, lymphoid tissue, and intestinal epithelium are especially vulnerable. The first of the cytotoxic agents to be generally used in neoplastic disease was *mechlorethamine hydrochloride* or *nitrogen mustard.*

**Mechlorethamine Hydrochloride (Nitrogen Mustard).** During World War II a number of nitrogen analogs of mustard gas (bis[2-chloroethyl] sulfide) were studied as vesicants. These compounds were designated the *nitrogen mustards.* After absorption in the animal body, both the sulfur and the nitrogen mustards produce cytotoxic actions on a variety of tissues. In a general way, cellular susceptibility to these substances is related to the degree of proliferative activity of the cells. The hematopoietic system is especially sensitive. This action is somewhat different from other known chemical agents and resembles in some respects the effect of roentgen rays on cells. Plant cells are influenced by these agents as well as animal cells. A logical extension of these observations was the study of these chemicals in neoplastic disease, particularly of lymphoid origin. The margin of safety in the use of the nitrogen mustards is narrow, and they must be employed with extreme caution clinically.

**The nitrogen mustards.** In aqueous media the nitrogen mustards as a class undergo transformation and reactions with biologic compounds, and their pharmacologic properties depend upon these reactions. The primary transformation which occurs is an intramolecular cyclization to form cyclic imonium cations.

Methyl-bis-(β-chloroethyl)-amine is stable in solution as the hydrochloride for hours, but in aqueous solution under physiologic conditions at pH 7.4 and 37°C. undergoes rapid intramolecular rearrangement with the loss of $Cl^-$ to form a cyclic onium cation as follows:



In the case of the β-chloroethyl tertiary amines the cyclic imonium group formed reacts readily with various anions and uncharged nucleophilic molecules such as DNA. This reactivity of the cyclic onium cation is responsible for the marked biologic activity of the nitrogen mustards. The nitrogen mustard (HN2), methylbis-(β-chlorethyl)-amine appears to offer therapeutic advantage in the lymphoma or Hodgkins' types of tumors. It is recognized in the Pharmacopeia as *Sterile Mechlorethamine Hydrochloride.*

**Pharmacologic action of mechlorethamine hydrochloride.** Mechlorethamine exhibits a selectivity for the *lymph nodes*, *spleen*, *bone marrow*, and intestinal epithelium. Its biologic effect may be considered as specifically *cytotoxic*. Cellular enzyme systems are inhibited and cell death ensues. Mechlorethamine is *nucleotoxic*. Mitosis and cell growth are retarded by its action. In sublethal doses the activity of mechlorethamine is confined largely to the foregoing effects.

Sublethal doses have a specific cytotoxic effect, especially on proliferative cells. Pathologic changes in tissue cells are specifically confined to the gastrointestinal mucosa and the blood-forming organs. The gastrointestinal effects are manifested by severe diarrhea. A lymphopenia, granulocytopenia, thrombocytopenia, and a moderate anemia are evidence of damage to blood-forming organs. Lymphoid tissue is involved, leading to a persistent lymphatic atrophy. Early changes in the bone marrow include swelling and alteration in the staining reaction of hematopoietic cells and a disappearance of mitotic activity. Eventually, almost complete aplasia results. When supralethal doses are given after protecting bone marrow by technics to be described later, neurotoxicity becomes apparent. This consists of dizziness, ringing in the ears, headache, and convulsions.

**Dosage and clinical use of mechlorethamine.** Mechlorethamine hydrochloride is administered in doses of 0.1 mg./kg. once daily for 4 consecutive days. The solution is prepared immediately before use and administered intravenously. The usual strength of the solution is 1 mg./ml. In order to minimize chemical trauma to the veins, in many clinics the agent is injected slowly into an infusion of normal saline solution which is being infused into the vein. The course of treatment may be repeated at a 4-week interval. Generally, the maximal number of courses is 5. Contact with the skin and mucous membranes must be avoided.

Nausea and vomiting are produced by the therapy. The gastrointestinal distress may be very severe. Pyridoxine or sedatives administered ½ hour after the injection may ameliorate the untoward effects. The antiemetic drugs such as Compazine are also useful in ameliorating the nausea produced by mechlorethamine. Weakness and anorexia are common after treatment. A moderate degree of leukopenia usually follows the treatment with mechlorethamine. Larger doses may produce severe *leukopenia*, *anemia*, *thrombocytopenia* and *hemorrhagic diathesis.*

Collective reports from 300 institutions describing the use of nitrogen mustard therapy in more than 2500 cases are now available. It is clear that because of the toxicity of nitrogen mustard therapy and unpleasant side effects, the *indiscriminate* trial in patients with inoperable cancer or in the terminal stages of the disease is unjustified. Its use should be confined to types of tumors known to respond to it.

Many neoplasms exhibit an increased arterial blood supply and increased capillary permeability upon arteriography. The intra-arterial injection of mechlorethamine directed at the tumor sites will supply a temporary increased concentration of the agent in the target area. Investigators have observed temporary improvement for months in patients with widespread visceral metastases involving the liver, kidneys, and lungs. The intra-arterial use of alkylating agents offers possibilities for a more intensive therapy at the neoplastic sites.

However, to be effective the alkylating agent would need to have a much shorter biologic half-life than HN2 (minutes). Seligman (1962) and Witten *et al.* (1962) designed alkylating agents with a biologic half-life that is a fraction part of a second. Their rationale is based upon administering a cytotoxic agent intra-arterially without concern for the danger of bone marrow depression caused by the agent returning on the venous side of the circulation. An agent with such a short half-life under clinical study at present is shown in the formula:

$$[BrCH_2CH_2S\text{-}CH_2CH_2CONHCH_2^-]_2 \text{ or S-182.}$$

Reinhard *et al.* (1950) reviewed the use of nitrogen mustard in Hodgkin's disease and lymphosarcoma. It is their opinion that roentgen therapy remains the treatment of choice for the

localized conditions of the diseases. Mechlorethamine, however, may serve as adjunct therapy in the diffuse form of the diseases and also if the lesions become "roentgen fast."

Hatch *et al.* (1956) summarized their findings in the treatment of nearly 200 cases of advanced carcinoma of the lung. There were immediate and delayed toxic reactions to the therapy, as previously described. They concluded that symptomatic relief was achieved in about half of the patients. These findings are comparable to those reported by other observers. They hold the view that mechlorethamine therapy in multiple courses is a valuable adjunct to deep roentgen-ray therapy in lung cancer. However, they further emphasize the palliative nature of the treatment and assert that the beneficial effects are only transient.

Several modifications of the molecule of the original nitrogen mustard have been synthesized. Different types of prosthetic groups can be attached to the reactive molecules to produce major differences in their chemical properties and pharmacologic responses. Many of these newer agents elicit less distressing side effects and have found a definite place in the treatment of leukemia. In the treatment of solid tumors, however, the results for the most part have been disappointing.

Cytotoxic agents are made more effective by protecting bone marrow. This has been achieved in several ways. Either the bone marrow of the extremities of children is protected by tourniquets until the injected alkylating agent is inactivated (Seligman *et al.*, 1962), or an intra-aortic balloon is inflated at the level of the diaphragm and the alkylating agent is injected intravenously above the diaphragm. This affords protection to the pelvic bone marrow of adults (Miller and Lawrence, 1961). Regional perfusion with pump-oxygenator equipment and isolation of a segment of the circulation allows local intensive treatment with the alkylating agents (Ryan *et al.*, 1958).

That the alkylating agent does not always need to be polyfunctional is demonstrated by the palliative action against ovarian carcinomatosis with ascites shown by the monofunctional agent, hemisulfur mustard, $HOCH_2CH_2SCH_2CH_2Cl$, Green (1959). This agent does not suppress the hematopoietic system, but is instead limited by neurotoxicity.

Attempts to bring a greater degree of specificity to the alkylating agents have been undertaken by Seligman *et al.* (1962) and Witten *et al.* (1962). By taking advantage of differences in enzymic activity of normal and neoplastic tissue, they have prepared alkylating agents with enzyme susceptible linkages. Upon hydrolysis of an ester or amide link, a toxic 2-armed alkylating agent is converted to a very much less toxic 1-armed mustard. Thus, tumors with less esterase activity than normal vital epithelial cells would be less able to detoxify these toxic agents. The abundant esterase in the circulating blood defeats the effectiveness of this rationale, but amidase is less abundant. It will be interesting to see whether this approach to making alkylating agents more effective will succeed.

The principal agents in this class are listed in table 57-1. Those which are used in leukemia are discussed in detail in chapter 45.

### ANTIMETABOLITES

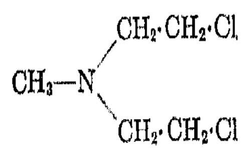
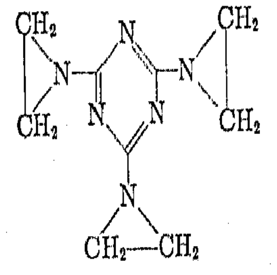
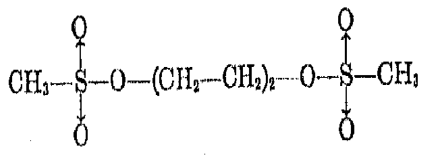
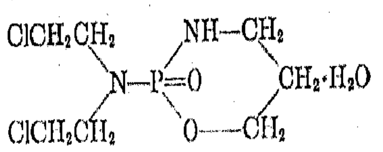
The antimetabolites of folic acid such as aminopterin and methotrexate are most effective in the treatment of leukemia in children, and their use is discussed in chapter 45. Similarly, 6-mercaptopurine, which likely interferes with the conversion of physiologic purines into nucleic acid, is most useful in the treatment of leukemia and is discussed under that heading. In most cases the antimetabolites have proved of little value in the treatment of solid tumors.

Li *et al.* (1958) reported a regression of choriocarcinoma of the uterus upon the administration of methotrexate at a high dosage level (15 to 25 mg. daily for 5 days). The medication caused a diminution of the excretion of the chorionic gonadotropin in the urine. Remission of the disease in several patients lasted more than 2 years. It is not possible, at present, to determine the consistency of response of metastatic choriocarcinoma to antimetabolite treatment; however, prolonged regression and possible cure of one type of cancer with antimetabolite therapy marks definitive progress in the field. It should be pointed out, however, that choriocarcinoma is a homologous tumor in the host since it arises from fetal cells of the placenta. This may be why chemotherapy is more effective than in other solid tumors of man.

Another promising report on antimetabolite therapy in cancer was reported by Ansfield and Curreri (1959) using 5-fluorouracil developed by Heidelberger *et al.* (1957). This antipyrimidine

TABLE 57-1

*Polyfunctional Alkylating Agents*

| Formulas | Derivatives of Clinical Interest | Usual Dose (Total Course or Daily) |
|---|---|---|
| Prototype compound | | |
|  Methyl-bis(β-chlorethylamine) | Methchloramine<br>Nitrogen mustard | 0.4 mg./kg. i.v. |
| | Nitromin | 500 mg. i.v. |
| | Chlorambucil (Leukeran) | 0.1 to 0.2 mg./kg. daily by by mouth |
| | Phenylalanine mustard<br>L-form (Melphalan)<br>DL-form (Sarcolysin) | 100 mg. i.v. |
|  Triethylenemelamine | Triethylenemelamine (TEM) | 0.12 mg./kg. i.v. 10 to 40 mg. a month, orally |
| | Triethylene thiophosphoramide (TSPA) Thio-TEPA | 0.8 to 1.0 mg./kg. i.v. |
|  $CH_3-\overset{O}{\underset{O}{S}}-O-(CH_2-CH_2)_2-O-\overset{O}{\underset{O}{S}}-CH_3$ Busulfan | Busulfan (Myleran) | 2 to 6 mg. daily |
|  Cyclophosphoramide | Cyclophosphoramide (Cytoxan) | 2 to 3 mg./kg. i.v. for 6 days |

appears to inhibit nucleic acid synthesis. The work of Ansfield and Curreri indicated that carcinoma of the breast, ovary, large bowel and rectum, and hepatoma were sensitive to 5-fluorouracil therapy. The antimetabolite appeared to exert no beneficial effect in carcinoma of the lung, stomach, or pancreas or in hypernephroma or malignant melanoma. The dosage schedule which was most effective in sensitive tumors was 15 mg./kg. daily for 5 days, followed by half doses given on alternate days until the appearance of toxic symptoms such as bone marrow depression and intestinal lesions. Maintenance dosage was ineffective and may have produced deleterious effects in the patients. Repeating the foregoing dosage regimen at monthly or at several monthly intervals was most effective and better tolerated by the patients. These workers emphasize the extreme toxicity of 5-fluorouracil and hold the view that although the drug elicits a tumor-suppressing action in some patients, not any of their patients was cured by its administration.

Ivy (1962) used 5-fluorouracil in 22 patients with active progressive disseminated carcinoma of the breast in which all other types of standard therapy had failed. Of this series 5 patients showed subjective and objective improvement. Ivy believes the improvement outweighs the side effects of the drug and recommends its use, when hormonal therapy fails, before resorting to hypophysectomy and adrenalectomy.

### ANTIBIOTICS

The use of the antibiotic azaserine as an adjunct in the treatment of leukemia is discussed in chapter 45. Other antibiotics (chapter 10) have been used with some degree of success in the treatment of solid tumors. The *actinomycins* are very toxic antibiotics obtained from *Streptomyces chrysomallus*. Their structures have been recently determined. The active agents in this group of antibiotics have 2 lactone groups in the polypeptide chain. The mechanism of their cytotoxic effects appears to be dependent upon the integrity of the red chromophore structure and the 2 lactone groups in the molecule. The most generally used members of this group are actinomycin C (Sanamycin) and actinomycin D.

The actinomycins are extremely toxic; the usual intravenous dose in man is in the order of 0.2 to 0.5 mg. Evidence of toxicity is manifested at a total dosage range of 0.075 mg./kg. (2 to 5 mg.). Actinomycin D is less toxic by mouth, but this is likely due to very poor absorption from the gastrointestinal tract. The toxic symptoms are oral ulcerations, skin eruptions, nausea and vomiting. Actinomycin may also produce leukopenia and thrombocytopenia. Extravasations into tissues at the site of injection evoke severe local reactions.

Actinomycin D has been found especially useful in the treatment of Wilms' tumor. It also appears to have a suppressing action in certain sarcomas. The mechanism of action of actinomycin D is obscure.

### ALKALOIDS

**Vinblastine Sulfate (Velban).** Vinblastine sulfate is the sulfate of a dimeric alkaloid obtained from *Vinca rosea* (the periwinkle). The alkaloid contains an indole and a hydroindole ring. The empirical formula is $C_{46}H_{68}N_4O_9 \cdot H_2SO_4 \cdot H_2O$. It occurs as a slightly yellow powder that is readily soluble in water. The aqueous solution should be stored at low temperatures to prevent decomposition.

**Mechanism of action.** The precise antineoplastic action of vinblastine has not been determined. However, indications are that the alkaloid acts as an antimetabolite likely interfering with the cellular utilization of glutamic acid. In animal and human cells the compound arrests mitosis in metaphase, likely by affecting the spindle apparatus.

**Clinical use of vinblastine.** The principal clinical applications of vinblastine at present appear to be in Hodgkins' disease and choriocarcinoma that is resistant to other drugs.

**Untoward effects and dosage of vinblastine.** Leukopenia, stomatitis, gastrointestinal distress, and alopecia are fairly common side effects of therapy with vinblastine. Weight loss, muscular pains, and generalized weakness have also been encountered. If the dosage schedule is not meticulously followed, central nervous system damage may occur, and death has resulted from the excessive use of the drug.

Vinblastine sulfate is given intravenously by injecting the prescribed dose dissolved in normal salt solution (1 mg. in 10 ml.) into the tubing through which 5 per cent dextrose solution is being infused into the vein. The first dose is usually 0.15 mg./kg. The white cell count is taken, and after 7 days if the count has returned to at least 4000, a second dose of 0.2 mg./kg. may be given. Maintenance therapy is given every 7 to 14 days of 0.1 to 0.15 mg./kg. according to the patient's improvement and the degree of leukopenia produced.

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# PART IX

## PHARMACOLOGIC AGENTS IN ALLERGIC DISEASES AND SUPPLEMENTAL THERAPEUTIC AIDS

## 58

## *Pharmacologic Agents in Allergic Diseases. The Antihistaminics*

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**Character of allergic diseases.** The allergic diseases are difficult to delineate because they represent altered reactions of the body associated with an antigen-antibody mechanism which is elusive in character. The antigen may be a commonly encountered substance or it may be exotic.

In like manner the antibody may or may not be readily demonstrable in the host. In addition, there is much confusion among allergists regarding the scope and terminology of the allergic diseases. For example, a number of diseases are suspected but not proved to be allergic in character, and diversified meanings are attached to such terms as anaphylaxis and idiosyncrasy. It is beyond our scope to discuss these important clinical problems, and the reader is referred to several excellent reviews (Feldberg and Loeser, 1954; Mayer, 1954; Rocha e Silva, 1955).

Pharmacologic treatment appears to have surpassed the knowledge of causative mechanisms in allergic diseases. The success associated with the medical use of the numerous antihistaminics, certain antiserotonin drugs, the sympathomimetic amines, aminophylline, and the corticosteroids in allergic states attests to this view. Attention will be given in this chapter to those drugs that are employed in the treatment of the allergic diseases. The pharmacology of many of these drugs has previously been considered.

The clinical manifestations of the allergic diseases may be conveniently grouped as: *respiratory*, including asthma and allergic rhinitis; *gastrointestinal*, involving lesions of the gastrointestinal tract, nausea, vomiting, and diarrhea; *nervous system involvement*, including the central nervous system and the peripheral nerves; and *cutaneous lesions*, including the urticarial and eczematous states and the many forms of contact dermatitis. In addition, numerous specific organs may be involved in allergic diseases. The concept has been proposed that the inciting factor or antigen in interaction with antibodies provokes allergic reactions in one or more "shock" organs; these reactions then produce the various clinical symptoms and lesions.

The incidence of allergic disease has been estimated to lie between 10 and 20 per cent of the population. There is believed to be an inherited complex of metabolic or enzymic characteristics that follows genetic patterns. Relatives of patients with allergic complaints constitute a valuable diagnostic clue. The low incidence of approximately 0.1 per cent of allergic diseases among patients in mental hospitals is remarkable.

Recognizing the numerous views regarding the various categories of allergic diseases one may briefly summarize these as follows:

**Respiratory allergies.** *Allergic rhinitis*, commonly called hay fever and manifested by spasmodic rhinorrhea, nasal congestion and sneezing, and frequently an associated conjunctivitis, is usually due to seasonal pollens and mold spores or both. Nonseasonal or perennial rhinitis is also designated as vasomotor rhinitis. The most important causes are environmental antigens including house dust, animal danders, feathers, mold spores, foods, chronic infections of the upper respiratory tract, and emotional tension states. Seasonal hay fever is usually severe, but the protracted nature of the perennial form produces greater disability. Frequently, the seasonal and perennial type occur in the same individual.

**Bronchial asthma** is characterized by recurrent attacks of dyspnea of a wheezing type resulting from the narrowing of the lumen of the smaller bronchioles.

This is the most serious of the allergic syndromes. The asthmatic paroxysm is a respiratory disturbance but is essentially an expiratory dyspnea. The expirations are forced and accompanied by a high pitched "wheeze." The causes of asthma are the same as those enumerated under seasonal and perennial rhinitis; in fact, all 3 manifestations of respiratory allergy frequently coexist, and the delineation of the varied etiology is often difficult. Special consideration is given to the pharmacologic agents employed in bronchial asthma in the last part of this chapter.

**Gastrointestinal symptoms of allergies.** Symptoms of nausea, vomiting, diarrhea, and abdominal pain can be most prominent when the gastrointestinal tract is the shock structure. However, angioneurotic edema of the lips, mouth, and esophagus may be the chief symptom. This type of allergy is ordinarily associated with food or drug antigens taken by mouth but this need not be the case. Chronic symptoms are more common than acute attacks. It is believed that in some cases endogenous allergens may be formed in the intestinal tract.

**Nervous system manifestations of allergies.** Involvement of the central nervous system in allergic diseases is suggested in clinical syndromes of persistent headaches and periodic headaches with vomiting, as in migraine and in cerebral hemiplegias. Neuritic symptoms of the peripheral nervous system have been ascribed to allergens by some workers. Involvement of the autonomic nervous system in the allergic process is also suggested. The allergic basis of symptoms ascribed to the nervous system is less clear than other clinical manifestations.

**Cutaneous lesions.** Urticaria, more commonly called hives, and angioneurotic edema are but 2 categories of allergic skin diseases. In the former, large allergic wheals develop in the dermis. In the latter condition there is a similar skin eruption with large areas of edema involving the subcutaneous structures. Allergic cutaneous lesions, characteristically itch, and pruritus are generally the first symptoms. Urticarial reactions may develop quickly and rapidly subside, only to reappear at the same site or at some other locus. Edematous swelling may involve the mucous membranes of the upper respiratory tract. Acute symptoms resulting from the closure of the glottis may necessitate immediate antidotal measures to prevent fatal asphyxia.

**The nature of allergens.** Specific etiology of the allergic diseases in addition to those mentioned includes drugs, foods, chronic infections, and stress phenomena (emotional tension) Nearly every drug produces in some individuals allergic manifestations. In addition, Lockey (1959) has pointed out that allergic reactions may be caused by coloring agents used in trace amounts in imparting distinctive colors to tablet dosage forms of many drugs.

Urticaria and angioneurotic edema may also occur in rheumatic fever, rheumatoid arthritis, lupus erythematosus, and periarteritis nodosa, diseases in which allergic mechanisms are presumably important. On the other hand, some substances cause fixed reactions. For example, phenolphthalein may produce a so-called fixed drug eruption of the skin. These skin lesions are pink-colored urticarial wheals which appear repeatedly on the same circumscribed areas of the skin when the drug is taken repeatedly.

Multiple allergic manifestations may occur when a patient is simultaneously sensitized to 2 or more agents that may have affinities for different shock organs.

There is a distressing lack of correlation between the chemical nature of allergens and the allergic diseases they elicit. As expressed by Mayer (1954), this is one of the basic credos of allergy, and it is also the allergists' cross of diagnosis.

Briefly, the concept of the allergic process may be illustrated as follows:

$$\text{Antigen} \xrightarrow{\text{provokes}} \text{specific antibodies}$$

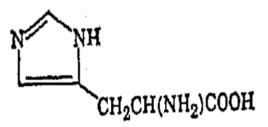
$$\begin{array}{c}\text{Antigen}\\ + \\ \text{Specific antibody}\end{array} \xrightarrow{\text{release}} \text{allergotoxin}$$

The allergotoxin evokes the tissue response. It may be histamine or a histamine-like substance or any of a large number of postulated agents. Pharmacologically, the histamine concept has been very fruitful, and based upon this premise the antihistaminic agents were evolved. Future investigations may demonstrate the presence of other specific substances which in turn may lead to better pharmacologic control of allergic states (Yonkman, 1950).

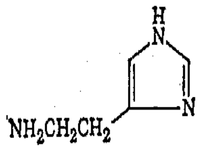
**Serotonin antagonists in allergy.** Serotonin has been implicated in anaphylactic or hypersensitivity reactions for a number of years. The discovery of antiserotonin drugs that are effective in treating pruritic dermatoses and preventing "histamine cephalgia" suggests that serotonin, like histamine, plays a role in allergic manifestations. The drugs that are used clinically as antiserotonin agents are considered in this chapter (Carr and Aste, 1961).

### THE PHARMACOLOGIC RESPONSES TO HISTAMINE

Histamine is an ubiquitous substance. It is found widely distributed in animal and plant tissues. *Pharmacologically, it is a potent agent and affects many structures of the body.* Histamine was discovered by Windaus and Vogt in 1907. It was prepared synthetically from iminazolylpropionic acid. Histamine is *β-iminazolyethylamine* and is closely related to the amino acid histidine from which it may be derived by decarboxylation as follows:



Histidine



Histamine

Pharmacologic interest was aroused in histamine by the isolation of the compound from ergot by Barger and Dale in 1910. They assigned the name "Ergamine" to the compound. Almost simultaneously the base was separated from soy beans. In 1912 Mellanby and Twort observed that the flora of the intestinal tract of man could decarboxylate histidine and produce histamine. L-histidine has been shown to be the precursor of bound histamine in the cat and other species by Schayer (1959) using $C^{14}$ L-histidine.

Barger and Dale (1910) isolated histamine from the intestinal mucosa. Abel and Kubota in 1919 isolated the base from the posterior lobe of the pituitary gland, liver, skeletal muscle, and other tissues (Abel, 1930). Best (1929) demonstrated the presence of histamine in many kinds of tissues. The histamine content of different tissues shows wide variation. There are also wide species differences. The blood of the horse, dog, cat, rat, as well as that of man, is low in histamine. Goat and rabbit blood contains relatively high concentrations. In most species the skin, lung, and intestines are high in histamine, whereas the kidney, pancreas, and spleen show a low histamine content. The physiologic significance of this distribution is not understood. Johnson (1957) holds the view that the histamine content of human skin is not related to skin disease or skin hypersensitivity reactions.

Hagen and Weiner (1959), Grossberg and Garcia-Arocha (1954), and others are of the opinion that histamine is bound to tissue cells in a very special way. Their experiments with the liberation of histamine from liver particulate fractions suggest that histamine is not bound to a tissue component by a primary chemical bond. Rather, histamine is most likely enclosed in a diffusible form within a mitochondrion-like particle. Thus, any change in the properties of the particle-cytoplasm interface would permit histamine to diffuse out. Such a change may be an increase in the permeability of the membrane or damage to the cell surface. Histamine appears to be located mainly in the mast cells of tissues, and it is proposed that the characteristic granules of these cells contain histamine. According to Bhattacharya and Lewis (1956) and others, compound 48/80 acts on mast cells, disrupting them, thereby releasing the histamine and 5-hydroxytryptamine (serotonin) they contain.

Ellinger (1935 *et seq.*) proposed that irradiation of the body by x-rays or ionizing radiations caused the liberation of histamine in amounts sufficient to produce the clinical manifestations of "radiation sickness" or "acute radiation syndrome." The latter condition represents the effects produced after exposure to lethal doses of ionizing radiations originating from nuclear fission. The pharmacologic and toxicologic effects of irradiation were described by Ellinger (1951) as related to histamine liberation from tissues.

In the following discussion of the pharmacodynamics of histamine emphasis is placed on the effects of histamine in animals. It must be stressed that there is wide variation in susceptibility to histamine in different species of animals. In addition, histamine is dangerous if injected into man even in low doses, and individuals are remarkably different in their degree of susceptibility to histamine. Knowledge of histamine effects in man is predicated upon the apparent release of histamine from its binding sites as a result of an allergic reaction.

**The effect of histamine on the circulation.** Histamine is not well absorbed from the gastrointestinal tract. When injected subcutaneously or intravenously in animals, histamine causes a precipitous fall in blood pressure which is transient if the dose is small. If, however, the solution is injected continuously or repetitiously, the blood pressure remains at a low level. The depressor response to histamine is due principally to *capillary dilatation.* The walls of the capillaries are now more permeable and the tissues become edematous. Circulation is greatly retarded. The phenomenon resembles anaphylactic shock. In the rabbit, histamine injections may produce vasoconstriction with a rise in blood pressure or vasodilatation with a corresponding fall in blood pressure. The pulmonary arteries are constricted by histamine. In the rabbit this effect may be sufficiently profound to obscure the generalized capillary dilatation. There are marked species variations in the response to histamine.

In a laboratory animal, *e.g.* dog, if one infuses into the circulation a diluted solution of histamine the blood pressure will fall to ½ or ⅓ of its normal level. The pressure remains low for a considerable period of time. If one injects a large volume of normal salt solution to supply the fluid lost to the circulation, the blood pressure rises gradually and returns to its normal level as the histamine is destroyed by tissue enzymes which modify or otherwise inactivate histamine.

Small doses of histamine have little effect upon the myocardium. The perfused mammalian heart is first slowed and then accelerated by perfusion with a histamine solution. Repeated intravenous injections of histamine will ultimately produce dilatation of the right side of the heart. This is

probably due to the increased resistance in the blood vessels in the lungs. Further administration of histamine may produce tissue changes in the heart.

**The effect of histamine on the bronchioles.** The intravenous or subcutaneous injection of histamine in animals produces a prompt contraction of bronchial musculature. The mucosa becomes swollen and edematous as occurs in bronchial asthma in man. Pulmonary emphysema may be produced. The pulmonary arteries are constricted by histamine in addition to its effect on the bronchial musculature.

The bronchial spasm produced by histamine, like the asthmatic spasm, is effectively antagonized by epinephrine or atropine.

**The effect of histamine on gastric and other secretions.** Injections of histamine in animals or man produce a marked stimulation in the secretion of gastric juice. The dose required to excite gastric secretion may be sufficiently small so as not to cause a fall in blood pressure. An intramuscular injection of 0.5 to 1 ml. of solution of histamine acid phosphate (1–1000) produces a prompt gastric secretion response in normal individuals or subjects with *pseudoachlorhydria.* In pernicious anemia patients the gastric response to histamine is not elicited, indicating the presence of true *achlorhydria.* This test is used diagnostically for the purpose of differentiating the two types of achlorhydria.

The maximal secretion of gastric juice after histamine injection occurs in patients in about 30 minutes, and the effect persists for approximately an hour and a half. The injection in most individuals produces headache, flushing of the face, some dizziness, and a wheal at the site of injection. The repeated injection of histamine in the cat and rabbit, owing to the increase in gastric acid secretion, will produce erosion of the gastric and duodenal mucosa and ulceration.

In animals salivary secretion is increased by histamine injections. The secretion from the submaxillary gland is blocked by atropine, but the secretion from the parotid gland is not affected by atropine. Pancreatic secretion is stimulated also by injections of histamine.

Lin *et al.* (1962) reviewed the possible roles played by histamine in gastric hydrochloric acid secretion. There is no proof that histamine is the hormone or the chemical mediator of gastric secretion, but obviously, histamine and certain specific chemical compounds related to histamine are capable of exciting HCl-secreting units of the gastric mucosa.

**The effect of histamine on the uterus.** The uteri of the cat, rabbit, and guinea pig are strongly contracted by very diluted solutions of histamine. The uterus of the rat, however, is relaxed by the drug. The human excised uterus is contracted by histamine, and when the drug is injected, the parturient or postpartum uterus is promptly and strongly contracted. The effect is transient.

**The urticarial response to histamine.** If histamine in diluted solution is applied to scarified skin, the area is first blanched, then capillary dilatation ensues, and a typical wheal is produced. The wheal is white and usually surrounded by a red border. In susceptible individuals a subcutaneous or intramuscular injection of 0.5 to 1 mg. of histamine may produce this same type reaction over large areas of the skin. The skin in the area of the injection becomes blanched. This is due to the mechanical expression of blood from the area by the pressure of the fluid injected. In a matter of 20 to 30 seconds the area becomes hyperemic owing to capillary and venule dilatation produced by contact with histamine. This is followed by a "red flare" caused by arteriolar dilatation in this area. This is mediated through axon local reflex action. Within a period of 1 to 3 minutes sufficient fluid has permeated the capillary walls to produce the swelling that causes the wheal. The wheal is characteristically blanched with a red periphery. The response of the skin to pressure with a blunt instrument may be simulated by injecting small doses of histamine intradermally.

Dale and Laidlaw (1910) called attention to the striking similarity between the response to histamine injections and anaphylactic shock reactions. The evidence appears to be quite convincing that histamine plays a role in the production of anaphylactic shock in the dog, guinea pig, and presumably other animals. The question as to the part played by histamine in producing allergy reactions in man has been investigated repeatedly. Many investigators have duplicated partially or entirely in man allergic reactions by the injection of histamine. A number of workers have found an increased histamine concentration or an increased concentration of a histamine-like substance in the blood of allergic persons. The occurrence of symptoms was found to parallel the histamine elevation in the blood. There is evidence of the liberation of histamine from human tissues upon suitable exposure to a specific allergen.

Eyring and Dougherty (1955), in reviewing the mechanisms of inflammation, consider the water of hydration on the sodium ion in the tissue cells to be pumped out of the cell. A resulting ion-permeability condition is then established so that small metabolic molecules accumulate inside the cell. The resulting osmotic pressure increase will cause swelling and may rupture cells. The identity of the substance which causes the pumping of the water of hydration of sodium ions is suspected to be histamine. It has been referred to as *the pump substance.* This theoretical concept has proved useful in understanding the inflammation chain reaction set off by the trans-membrane gradient associated with the liberation of the pump substance.

Owing to the fact that the view of the predominant role of histamine in allergic reactions is not shared by other investigators, one is convinced that the matter is not settled. It appears that histamine plays an important role in many allergic responses. It is probably the principal one of many factors which will be revealed upon further investigation.

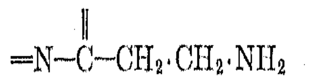
**Histamine headaches.** There is a definite type of headache observed in numerous individuals to which the name *"histaminic cephalgia"* has been assigned. It is well known that in many susceptible individuals the injection of histamine will produce definite headache. This has led to the view that histamine is an etiologic factor in the production of this type of headache. In certain cases relief is produced by administering repeatedly sub-effective doses of histamine and establishing in the patient a tolerance for the compound. The headaches begin in the latter decades of life and are of short duration. The pain is sufficiently intense to awaken one from sleep. The pain and tenderness are confined to the distribution of the external carotid artery. It involves the eye, temple, neck, and face. There is no nausea or visual disturbance as occurs with migraine.

It has been proposed that histamine headaches result from an increase in the amplitude of pulsations of the intracranial arteries. Normal persons experience a slight increase in the amplitude of the pulsations of the temporal artery. Patients who are subject to histamine headaches upon the injection of histamine experience a much greater increase in the amplitude of the pulsations of the temporal artery. The headache is relieved readily by the antihistaminic drugs.

There is speculation that has been advanced that psychotic patients may have some abnormal form of histamine metabolism. Some workers have reported low blood histamine levels in psychotics. These observations may coincide with the low incidence of allergic diseases in the mentally ill.

### HISTAMINE ANTAGONISTS

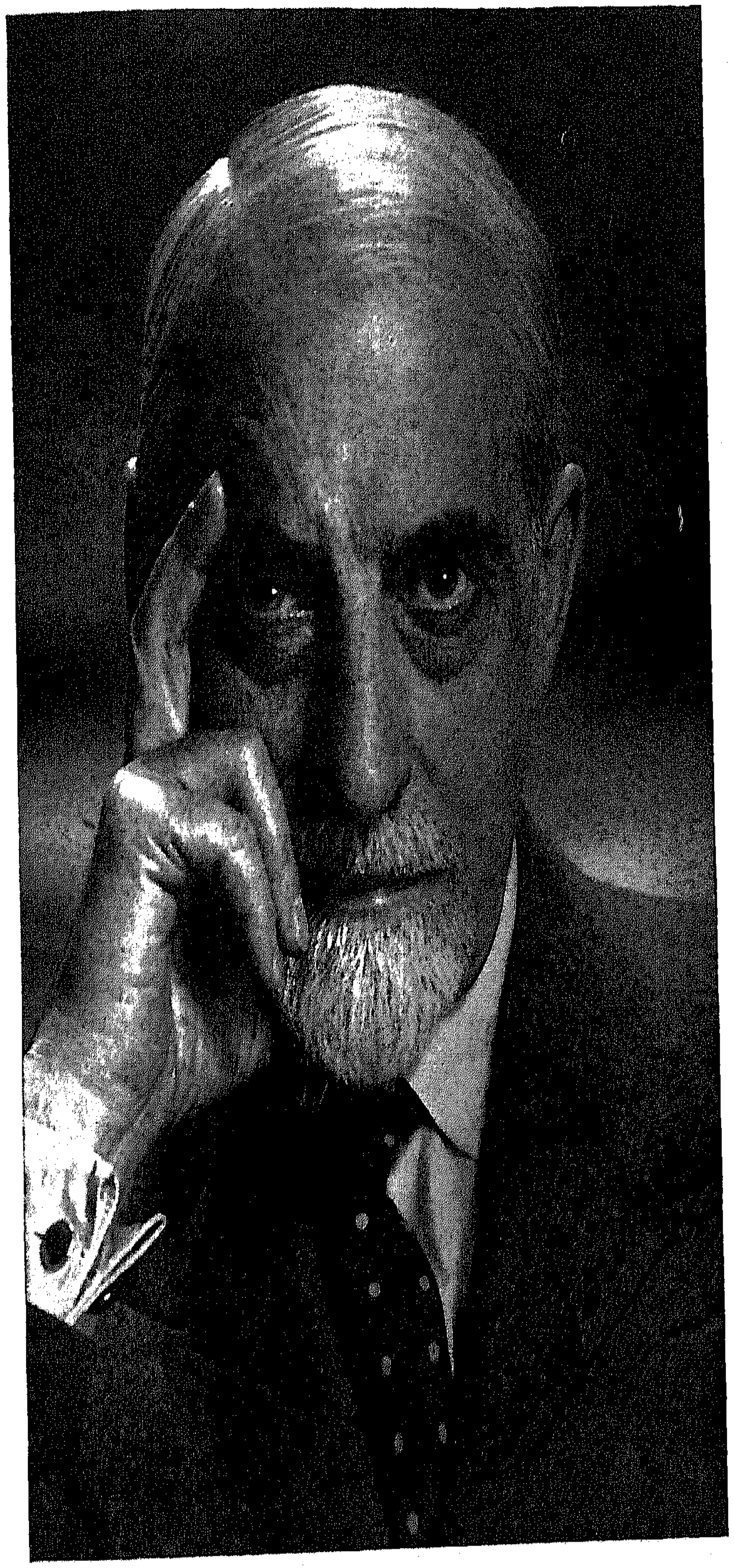
**Histamine specificity.** The foregoing paragraphs have indicated the multiplicity of the tissue responses provoked by the histamine molecule. Many attempts have been made to intensify the action of histamine and to modify its effects by change in molecular structure. These researches have shed light on the specificity of the histamine structure necessary to elicit the characteristic effects. Modification of the structure of the molecule which destroys the


$$=\!N-\overset{\|}{C}-CH_2\cdot CH_2\cdot NH_2$$

fragment causes the histamine activity to vanish. This architectural feature of the molecule appears to be essential for adsorption of histamine on the receptor centers of the target cells.

From what has been written regarding the pharmacologic responses to histamine, it is obvious that excessive histamine levels or hypersensitivity to this substance produce a variety of disconcerting symptoms. Among these which have been mentioned are urticaria, hay fever, histaminic asthma, and headache. It is therefore of great clinical importance to have available agents which will effectively antagonize the action of histamine. When one considers the various types of actions elicited by histamine, it becomes evident that the production of a substance to combat successfully all of these effects is difficult. Frequently several agents must be used. Therapeutically, the most successful histamine antagonists are the antihistaminic drugs.

**Metabolism of histamine.** Best (1929) demonstrated the presence of an enzyme in certain tissues capable of destroying histamine. This enzyme is called *histaminase* or *diamine oxidase* (Zeller, 1938). Schayer *et al.* (1956) and Brown *et al.* (1959) have described another enzyme, imidazole-N-methyl transferase, which appears to be of paramount importance in histamine metabo-



ERNEST FOURNEAU

1872–1950

*Eminent French scientist who prepared some of the first antihistaminic compounds*

"It was known in ancient times that in the bodies of animals there were certain glands that possessed toxic or curative properties."

lism. Ring N-methylation is the principal pathway of histamine metabolism in a variety of mammalian species including man, according to these findings. Adenosylmethionine, synthesized from ATP and methionine, is the donor of the active methyl group for the conversion of histamine to methyl histamine. As a result of diamine oxidase activity, deamination takes place, and imidazole-4-acetic acid and its riboside, 1-ribosylimidazole-4(5)-acetic acid are excreted in the urine. Imidazole-N-methyl transferase methylates histamine on the ring nitrogen remote from the side chain, to give 1-methyl-4-($\beta$-aminoethyl) imidazole which yields 1-methylimidazole-4-acetic acid. Following histamine injection, this latter substance is excreted in the largest amount in the urine of rabbits, cats, mice, dogs and man (Schayer, 1956 and 1959). The role the antihistaminic drugs might play in the metabolism of histamine has not been explored.

**Histamine analogs.** A number of compounds have been prepared that resemble histamine chemically (Lin *et al.*, 1962). These agents may mimic the effects of histamine or, because of structural similarities, may block the action of histamine. The antihistaminic drugs might be said to have a partial structural resemblance to histamine. A diamine oxidase inhibitor has been discovered that has many of the actions of histamine when administered orally. This drug is betahistine.

*Betahistine Hydrochloride* (*Serc*) is a 2-(2-methylaminoethyl) pyridine dihydrochloride. It is said to be active orally in doses of 4 mg. 4 times a day in the treatment of histaminic cephalgia and other disease states where histamine has been implicated. It is discussed in chapter 35. Its place in therapy remains to be established. It is not used in the treatment of allergic diseases.

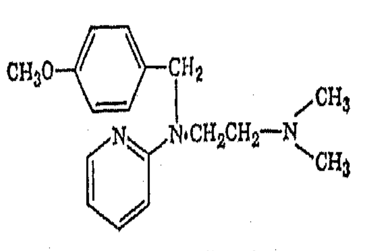
*Betazol Hydrochloride, U.S.P.* (*Histolog*) is an analog of histamine that stimulates gastric secretion like histamine.

### The Antihistaminic Drugs

There are a large number of synthetic organic compounds, most of them derivatives of ethylamine, which exhibit a specific antagonism to histamine *in vivo* and *in vitro*. All of these substances appear to have one common pharmacologic characteristic, *i.e., they compete with histamine in attachment to the cell receptors*. Thus, these substances block or obliterate the activity of histamine in living tissues.

The exact role played by the antihistaminics in the clinical relief of symptoms in allergic states is not defined. Some clinicians consider the sedative action which these drugs elicit to be the cause of their effectiveness. It is clear that the antihistaminics diminish capillary permeability, which is augmented by the allergic response involving the release of histamine. Until more information is available concerning the true function of histamine in normal and abnormal physiology of the body, a definitive statement cannot be made concerning the mechanism of action of these drugs.

**Discovery of the antihistaminic agents.** In 1933 Fourneau and Bovet discovered that certain phenolic ethers possessed antihistaminic properties. These compounds would protect guinea pigs against 2 lethal doses of histamine; however, they were quite toxic. Staub (1939) found that compounds with an ethylamine side chain attached to a benzene ring through a nitrogen atom were more effective antihistaminics, but these substances were too toxic for therapeutic use. Halpern (1942) continued these studies and finally succeeded in making N-phenyl-N-benzyl-N′-dimethylethylenediamine or Antergan. This drug proved to be the first successful antihistaminic drug. Later it was modified and the French drug Neo-Antergan was made. Neo-Antergan is now known as pyrilamine. Its structure is shown as typical of many antihistaminic drugs that have been synthesized in the past 25 years (Bovet, 1950).

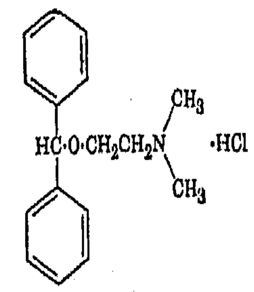


Pyrilamine, U.S.P.

These discoveries paved the way for the synthesis of superior drugs possessing antihistaminic properties. In the United States diphenylhydramine or Benadryl was reported in 1945 and tripelennamine or Pyribenzamine in 1946. Because these 2 drugs are typical of the series, their pharmacology is discussed in detail.

**Diphenhydramine Hydrochloride, U.S.P. (Benadryl hydrochloride).** Loew *et al.* (1945) studied a large number of synthetic compounds exhibiting antihistaminic activity. Diphenhydramine was found to be outstanding in the series. One of their criteria for measurement of effectiveness was the capacity of the substances to protect guinea pigs against exposure to a histamine aerosol. The antihistaminics were administered parenterally or orally. Without the previous injection of an antihistaminic drug, normal guinea pigs upon exposure to the histamine aerosol rapidly die from acute bronchoconstriction and the resulting asphyxia. By this test, diphenhydramine was found to be 2 to 4 times as active as many of the compounds of similar structure that were tested. It was 30 times more effective than aminophylline.

Chemically diphenhydramine is a substituted benzyl ether as shown in the accompanying formula. It is $\beta$-dimethylaminoethyl benzhydryl ether hydrochloride.



Diphenhydramine Hydrochloride, U.S.P.

Diphenhydramine hydrochloride occurs as a white crystalline powder. It is stable in the air. The compound emits a characteristic odor and elicits a bitter taste. It is very soluble in water.

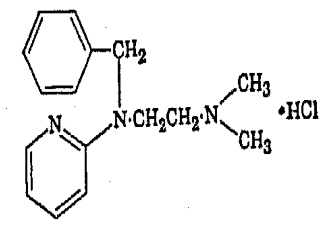
Wells (1950) showed that diphenhydramine was capable of preventing most of the depressor response to histamine in the anesthetized dog. A quantitative relationship appeared to exist. He showed that a constant percentage of any dose of histamine administered is antagonized by a given dose of diphenhydramine. If one plots the per cent inhibition of the fall of blood pressure against the dose of diphenhydramine the *dose-response* curve assumes the shape of a rectangular hyperbola. The inhibition increases sharply at low doses of diphenhydramine, and at a dose of about 1 mg./kg. the curve rapidly approaches the base line, showing about 97 per cent inhibition. This study points out that this type of dose-response curve suggests that *diphenhydramine exerts antihistaminic action through adsorption phenomenon on the target cells.* The data correlate well with the Langmuir adsorption isotherm.

Loew *et al.* (1946) measured the spasmolytic activity of diphenhydramine in antagonizing the spasm of an excised guinea pig's ileal muscle induced by histamine, barium chloride, or acetylcholine bromide. Diphenhydramine is spasmolytic when the spasm is produced by agents other than histamine; therefore the substance is not entirely specific. Nevertheless, the specificity of diphenhydramine for histamine on the guinea pig's ileum approaches the selectivity that atropine exhibits for acetylcholine.

Diphenhydramine, when injected intravenously in dogs in doses equal to and greater than comparable therapeutic doses in man, elicits a primary vascular depression followed by a rise in arterial pressure. In therapeutic equivalent doses the drug does not produce significant changes in respiration. At supratherapeutic dosage levels diphenhydramine causes respiratory depression.

Diphenhydramine in combination with 8-chlorotheophylline is the antimotion sickness drug dimenhydrinate, page 466.

**Tripelennamine Hydrochloride, U.S.P. (Pyribenzamine hydrochloride, PBZ).** Chemically, tripelennamine is related to diphenhydramine, but like pyrilamine contains a pyridine nucleus as shown by the accompanying formula. It is N′-$\alpha$-pyridyl-N′-benzyl-N-dimethylethylenediamine hydrochloride.



Tripelennamine Hydrochloride, U.S.P.

Tripelennamine hydrochloride is a white crystalline powder, stable in the air. It is freely soluble in water.

Tripelennamine is a powerful antihistaminic. It is capable of protecting guinea pigs against 100 lethal doses of histamine. It will antagonize effectively the action of histamine on such structures as the rabbit and guinea pig intestine, the guinea pig uterus, isolated lungs, and bronchi. The pharmacologic responses and acute and chronic toxicity of tripelennamine were extensively investigated by Yonkman *et al.* (1947).

The action of tripelennamine in antagonizing the depressor and bronchial constrictor responses of histamine is shown by Yonkman *et al.* (1947) in figure 58-1. This figure illustrates the typical pharmacologic effects of antihistaminic drugs in antagonizing the actions of histamine on blood pressure and bronchial constriction.

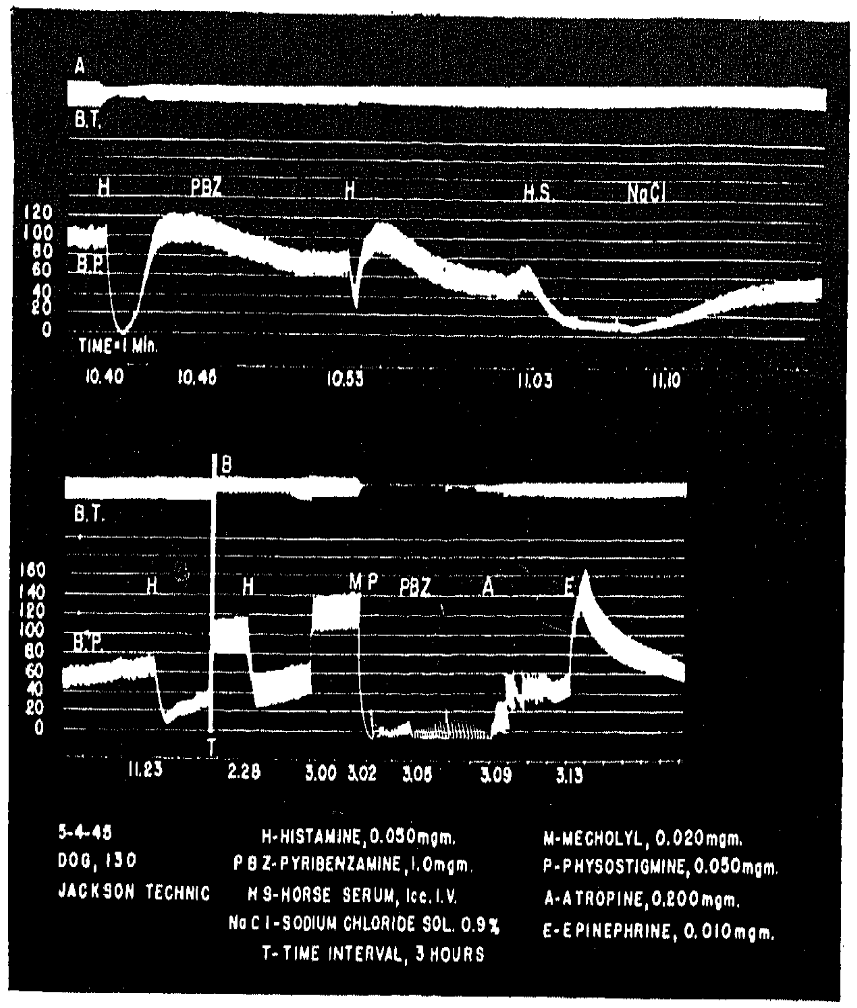


FIG. 58-1. Antagonism of Pyribenzamine to histamine on the blood pressure and bronchial constriction.

"Dog, 10.1 kg., sensitized to horse serum, 5 ml., intravenously and 5 ml. intramuscularly on 4-13-45. Pentobarbital anesthesia. Jackson plethysmograph. From above downward: bronchial tonus, arterial pressure, time in 5 second intervals. The bronchial constriction produced by histamine phosphate, 50 micrograms, was inhibited by Pyribenzamine, 1.0 mg., which simultaneously had some inhibitory effects on the acute hypotension produced by histamine and no prophylactic action against horse serum-induced hypotension. Physiologic sodium chloride solution was necessary to restore arterial pressure. Pyribenzamine, intracardially, was without benefit against acute hypotension following Mecholyl, 20 micrograms, and physostigmine, 50 micrograms, whereas, atropine sulfate, 0.200 mg. and epinephrine 0.010 mg. returned arterial pressure toward normal. Bronchial tonus, increased to maximum by Mecholyl and physostigmine, was only partially relieved by Pyribenzamine but returned to normal with atropine and epinephrine. Between A and B a time interval of approximately 3 hours elapsed during which 5 doses of histamine, 50 micrograms, and dihydrobetaerythroidin, 3 mg., were exercised." (From F. F. Yonkman, E. Opperheimer, B. Rennick, and E. Pettet: J. Pharmacol. & Exper. Therap., **89**: 31, 1947).

**Other antihistaminic drugs.** A large number of antihistaminic agents have been introduced into therapeutics. A list of these drugs, their various names, sources and dosage forms is given in table 58-1. It is impossible to give an account of the pharmacology of the individual drugs in a textbook of this character. For this reason these drugs are discussed as a group in the following sections.

The phenothiazine derivatives useful in mental illness and motion sickness are effective antihistaminic agents. Methoxypromazine (Tentone) and promethazine (Phenergan) are minor tranquilizers useful in anxiety and tension states. They are also of value as antihistaminic drugs in urticaria and allergic rhinitis.

Trimeprazine (Temaril) is *d,l*-10-(3-dimethylamino-2-methylpropyl)-phenothiazine. This compound is more active than promethazine and somewhat less active than chlorpromazine in protecting guinea pigs against histamine-induced bronchospasm. Its tranquilizing properties are of a low order. Its chief use is as an antipruritic drug. It is not known if its value as a drug to relieve itching is related to its antihistaminic or antiserotonin properties. It is recommended exclu-

TABLE 58-1

*Currently Used Antihistaminic Preparations*

| Trade Name | Generic Name | Dosage Forms |
|---|---|---|
| Actidil (Burroughs Wellcome) | Triprolidine HCl | Tablets: 2.5 mg.; Syrup: 1.25 mg./5 ml. |
| Allecur (Roerig) | Clemizole HCl | Tablets: 20, 40, and 50 mg. |
| Ambodryl (Parke, Davis) | Bromodiphenhydramine HCl | Kapseals: 25 mg.; Parenteral (i.v. or i.m.) 10-ml. vials, 5 mg./ml. Elixir: 10 mg./4 ml. |
| Anahist (Anahist) | Thonzylamine HCl U.S.P. | Tablets: 25, 50, and 100 mg. |
| Anthallan (Medico-Chemico) | Dibutylaminomethyltrihydroxybenzofuranone | Capsules: 85 mg. |
| Antistine (Ciba) | Antazoline HCl U.S.P. | Solution (*nasal*): 5 mg./ml. |
| Benadryl (Parke, Davis) | Diphenhydramine HCl U.S.P. | Capsules: 25 and 50 mg.; Kapseals and Emplets: 50 mg.; Elixir: 10 mg./4 ml.; Parenteral: 10- and 30-ml. vials, 10 mg./ml.; Benadryl HCl vials: ½ oz.; Kapseals: 50 mg. + 10 mg. ephedrine sulfate |
| Chlor-Trimeton Maleate (Schering) | Chlorpheniramine maleate U.S.P. | Tablets: 4 mg.; Repetabs: 8 and 12 mg.; Parenteral: 1-ml. ampul, 10 mg./ml.; 2-ml. ampul, 100 mg./ml.; Syrup: 2 mg./4 ml. |
| Clistin Maleate (McNeil) | Carbinoxamine maleate | Tablets: 4 mg.; R-A Tablets: 8 and 12 mg.; Elixir: 4 mg./5 ml. |
| Copsamine (Durst) | Pyrilamine maleate U.S.P. | Tablets: 25 and 50 mg. |
| Co-Pyronil (Lilly) | Pyrrobutamine phosphate | Pulvules: 15 mg. Pyronil + 25 mg. Histadyl + 12.5 mg. Clopane HCl; Pulvules (*Pediatric*): One-half strength; Suspension: 7.5 mg. + 12.5 mg. + 6.25 mg./5 ml. |
| Decapryn (Merrell) | Doxylamine succinate U.S.P. | Tablets: 12.5 and 25 mg.; Syrup: 6.25 mg./5 ml. |
| Diafen (Riker) | Diphenylpyraline HCl | Sustained release capsules: 5 mg.; Tablets: 2 mg. |
| Diatrine HCl (Warner-Chilcott | Methaphenilene HCl N.F. | Tablets: 50 mg. |
| Dibistine (Ciba) | | Tablets: 50 mg. antazoline HCl + 25 mg. tripelennamine HCl |
| Dimetane (Robbins) | Brompheniramine maleate | Tablets: 4 mg.; Sustained release tablets: 12 mg.; Elixir: 0.4 mg./ml.; Ampul: 10 mg./ml.; 200 mg./2 ml. |
| Diminic (Durst) | | Tablets: 25 mg. pyrilamine maleate + 25 mg. methapyrilene HCl |
| Di-Paralene HCl (Abbott) | Chlorcyclizine HCl U.S.P. | Tablets: 25 and 50 mg. |
| Disomer (White) | Dexbrompheniramine maleate | Tablets: 2 mg.; Syrup: 0.4 mg./ml. |
| Dozar (Tutag) | Methapyrilene HCl | Capsules: 25, 50, and 100 mg. |
| Forhistal (Ciba) | Dimethindene maleate | Drops (*oral*): 0.8 mg./ml.; Syrup: 0.2 mg./ml.; Tablets: 1 mg.; Tablets: (sustained release) 2.5 mg. |
| Hispril (S.K.F.) | Diphenylpyraline HCl | Capsules: (sustained release) 5 mg.; Tablets: 2 mg. |
| Hista-Clopane (Lilly) | | Pulvules: 25 mg. Histadyl + 12.5 mg. Clopane HCl; Solution: Histadyl 0.5% + Clopane HCl 0.5% |

TABLE 58-1—*Continued*

| Trade Name | Generic Name | Dosage Forms |
|---|---|---|
| Histadyl (Lilly) | Methapyrilene HCl | Pulvules: 25, 50 and 100 mg.; Syrup: 6 mg. fumarate (4 mg. hydrochloride)/ml.; Parenteral: 1- and 10-ml. vials, 20 mg./ml.; Solution 5%; Ointment Ophthalmic 5%; Pulvules: 25 mg. + 8 mg. ephedrine HCl. |
| Hydryllin (Searle) | | Tablets: 25 mg. diphenhydramine + 100 mg. aminophylline; Elixir: 12.5 mg. diphenhydramine + 100 mg. aminophylline/4 ml. |
| Inhiston (Union) | Pheniramine maleate N.F. | Tablets: 40 mg. |
| Neo-Antergan Maleate (Merck, Sharp & Dohme) | Pyrilamine maleate U.S.P. | Tablets: 25 and 50 mg. |
| Neohetramine (Warner-Chilcott) | Thonzylamine HCl U.S.P. | Tablets: 25, 50 and 100 mg. |
| Novahistine (Pitman-Moore) | | Tablets: 12.5 mg. pheniramine maleate + 5 mg. phenylephrine HCl; Elixir: 12.5 mg. pheniramine maleate + 5 mg. phenylephrine HCl/5 ml. |
| Paraminyl Maleate (Buffington) | Pyrilamine maleate U.S.P. | Tablets: 25 and 50 mg. |
| Perazil (Burroughs Wellcome) | Chlorcyclizine HCl U.S.P. | Tablets: 25 and 50 mg. |
| Phenergan (Wyeth) | Promethazine N.F. | Tablets: 12.5 mg.; Syrup: 6.25./5 ml. |
| Plimasin (Ciba) | | Tablets: 25 mg. tripelennamine HCl + 5 mg. methylphenidyl acetate |
| Polaramine (Schering) | Dexchlorpheniramine maleate | Tablets: 2 mg.; Syrup: 0.4 mg./ml. Repetabs: 4 and 6 mg. |
| Pyramal Maleate (Columbus) | Pyrilamine maleate U.S.P. | Tablets: 25 and 50 mg. |
| Pyra-Maleate (Vanpelt-Brown) | Pyrilamine maleate U.S.P. | Tablets: 25 and 50 mg. |
| Pyribenzamine Citrate (Ciba) | Tripelennamine citrate | Elixir: 7.5 mg./ml. |
| Pyribenzamine HCl (Ciba) | Tripelennamine HCl U.S.P. | Tablets: 25 and 50 mg.; D.A. Tablets: 50 mg.; Solution (*nasal*): 0.5%; Elixir: 7.5 mg. citrate (5 mg. hydrochloride)/ml.; Tablets: 25 mg. + 12 mg. ephedrine sulf.; Parenteral (i.v. or i.m.): 1-ml. ampuls, 25 mg./ml. |
| Pyronil (Lilly) | Pyrrobutamine phosphate | Tablets: 15 mg. |
| Pyrrolazote (Upjohn) | Pyrathiazine HCl U.S.P. | Tablets: 25 and 50 mg., (laminated tablets) 50 mg. |
| Semikon HCl (Massengill) | Methapyrilene HCl U.S.P. | Tablets: 25 and 50 mg. |
| Statomin Maleate (Bowman Bros.) | Pyrilamine maleate U.S.P. | Tablets: 12.5 and 25 mg.; Ampul: 25 mg./ml. |
| Tacaryl (Mead Johnson) | Methdilazine HCl | Tablets: 4 and 8 mg.; Syrup: 0.8 mg./ml. |
| Tagathen (Lederle) | Chlorothen citrate N.F. | Tablets: 25 mg. |
| Teldrin Spansule (S.K.F.) | Chlorpheniramine maleate U.S.P. | Capsules: (sustained release) 8 and 12 mg. |
| Temaril (S.K.F.) | Trimeprazine tartrate | Capsule: (sustained release) 5 mg.; Syrup: 0.5 mg./ml.; Tablets: 2.5 mg. |

TABLE 58-1 (*Continued*)

| Trade Name | Generic Name | Dosage Forms |
|---|---|---|
| Thenfadil HCl (Winthrop-Stearns) | Thenyldiamine HCl U.S.P. | Tablets: 15 mg.; Tablets-SA: 30 mg. |
| Thenylene HCl (Abbott) | Methapyrilene HCl U.S.P. | Tablets: 25, 50 and 100 mg.; Cream: 2% |
| Thephorin (Hoffmann-La Roche) | Phenindamine tartrate U.S.P. | Tablets: 10 and 25 mg.; Syrup: 10 mg./4 ml. |
| Thylogen Maleate (Rorer) | Pyrilamine maleate U.S.P. | Tablets: 25 and 50 mg. |
| Trimeton Maleate (Schering) | Pheniramine maleate N.F. (prophenpyridamine maleate) | Tablets: 25 mg.; Elixir: 7.5 mg./4 ml. |

sively for the symptomatic relief of mild and severe pruritus.

The usual dosage of trimeprazine is 5 mg. at bedtime and 2.5 mg. at breakfast and lunch. Low doses are usually effective, but the dose should be adjusted according to the severity of the symptoms and the response of the patient. Side effects of drowsiness, dizziness, dryness of mucous membranes, and gastrointestinal disturbances have been reported. As with any phenothiazine derivative, trimeprazine should be administered with caution. Patients should be watched for the possible occurrence of agranulocytosis, hypotension or parkinsonian-like symptoms, especially if the drug is administered for longer than 1 month.

### PHARMACOLOGY OF THE ANTIHISTAMINIC DRUGS

**Absorption, fate, and excretion of the antihistaminics.** The investigations designed to determine the absorption, fate, and excretion of the antihistaminic drugs permit several generalizations. The symptomatic relief after the oral administration of the drugs occurs within 20 to 45 minutes. This indicates rather rapid absorption from the gastrointestinal tract. Inactivation or excretion appears to occur within 3 to 4 hours after a single dose because the effects of the drugs usually disappear within this time period. To our knowledge no observation has indicated that the drugs give rise to cumulative effects. This bespeaks a comparatively short period of excretion or inactivation.

After subcutaneous injection of diphenhydramine into rats and guinea pigs, the highest concentrations are found in the lungs. Progressively lower levels are observed in the spleen, kidney, brain, liver, and muscle. The liver is capable of degrading diphenhydramine in all species studied. In the rat, the lung is also capable of catabolizing the drug; however, to a lesser extent than the liver. A similar distribution pattern was found for tripelennamine in rats. The compound is metabolized chiefly in the liver.

Weinman and Geissman (1959) studied the metabolism of $C^{14}$-labeled tripelennamine hydrochloride in guinea pigs and found 1 hour after injection all tissues examined contained radioactivity, and ⅙ to ½ of the $C^{14}$ was located in excretory pathways. Over 90 per cent of the drug was eventually excreted in the urine. They postulated that a cycle of elimination through the bile and reabsorption from the intestine takes place, but the major part of the drug is excreted in the urine. The urinary excretion products are hydroxy derivatives probably conjugated with glucuronic acid.

**Effects of antihistaminics on the central nervous system.** Many workers have observed that these agents elicit a depressant effect. The antihistaminic drugs increase the depth of barbiturate narcosis and its duration. Promethazine, diphenhydramine, antazoline, and chlorpheniramine have been observed to be the most potent in this regard. Phenindamine, tripelennamine, and pheniramine are less active. These effects have been observed in the clinical use of these drugs.

The mechanism of the central nervous system depression produced by the antihistaminic drugs is obscure. They do possess some anticholinergic properties, and their atropine-like action is quite prominent. There may be some association between these 2 effects. Numerous workers have demonstrated clinical benefits in parkinsonism. It has been found that antihistaminic potency may be changed without influencing the atropine-like activity, indicating that these 2 actions may be separated. Most of these compounds produce an increase in the central nervous system depression of pentobarbital in moderate doses; toxic doses produce excitement and convulsions. Certain compounds elicit depression and not convulsive seizures in lethal doses. The antihistaminics have not found a prominent place in the treatment of parkinsonism.

Churchill and Gammon (1949) reported that tripelennamine increased electrical discharges from the cortex in *petit mal* patients and augmented the incidence of seizures. On the other hand, diphenhydramine produced the opposite effect. These observations, which may be extended to other antihistaminics, indicate sharp differences in excitatory and depressant actions of these drugs. The significance of these findings must await a clearer understanding of the role of acetylcholine and histamine in brain function and metabolism. Individual susceptibility to a specific antihistaminic drug varies to a very significant degree. In addition, different drugs in this series are tolerated differently by a particular patient. The clinical implications of these facts are discussed under the therapeutic uses of these drugs.

**Miscellaneous actions of the antihistaminics.** Many of the antihistaminic drugs possess local anesthetic properties. Their potency in certain cases may exceed that of procaine. Some of the antihistaminics have significant fungistatic action.

**Use of antihistaminics in blood transfusions.** Several reports have appeared that indicate that injectable antihistaminic drugs are useful in preventing allergic and pyrogenic blood transfusion reactions. Stephan *et al.* (1955) point out that the common dangers associated with the intravenous injection of whole blood involve among others, allergic and anaphylactic reactions and so called "pyrogenic" reactions. This latter term usually is limited to mean substances derived from bacteria, but it may include many chemicals and materials used in blood transfusion. These substances may be allergens for some individuals. True allergy and anaphylaxis are associated with blood transfusions and are believed to result from the passive transfer of substances via the donor's blood. If it is agreed that allergic and anaphylactic reactions are related to the release of histamine and its action on receptor cells, then such reactions might be prevented by the administration of antihistaminic drugs. There is less reason to believe that pyrogenic reactions may be inhibited by these agents.

In a study of this matter, Stephan and his associates found that the prophylactic administration of tripelennamine reduced significantly the incidence of pyrogenic reactions and allergic type reactions in transfusion therapy. Wilhelm *et al.* (1955) in a similar study found that 50 mg. of diphenhydramine hydrochloride per unit of whole blood would eliminate allergic transfusion reactions but had no apparent effect on the incidence of pyrogenic reactions.

These observations suggest that unfavorable reactions resulting occasionally from blood transfusion therapy can be suppressed by the use of the antihistaminic agents in this manner. More extensive clinical trials are indicated.

### The Therapeutic Use of the Antihistaminics

The antihistaminics are useful in bringing about symptomatic relief in those allergic states that most closely resemble reactions to histamine. In general, the greatest effectiveness has been obtained in patients with urticarial reactions, angiodermatitis, allergic rhinitis, and inhalant asthma owing to pollens, dust, and animal dander. These drugs are less effective in infective rhinitis and bronchial asthma. These drugs are also relatively ineffective in serum sickness, which is a reaction characterized by fever and urticaria following the injection of a foreign serum.

An antihistaminic would be useful in those clinical entities where histamine is the inciting agent. Prominent among these would be lesions of the skin involving itching. Histamine may be considered to be the inciting factor where there are inflammatory skin changes associated with intense itching. In such conditions the antihistaminic drugs have been most useful. It should be pointed out that these drugs are palliative in action, and symptoms recur if the drug is discontinued.

There are many comparative studies of the effectiveness of the antihistaminics in the literature. Different antihistaminics are more or less effective in different people. Unsatisfactory clinical response may be obtained with a particular drug; by substituting another antihistaminic a favorable effect may be obtained. It would be regrettable to give a patient only partial relief when complete effectiveness may be possible by substituting another drug of the same series.

Dosage of the antihistaminics is a special problem. The average dose may provide only partial relief, whereas a slight increase in the daily dose may give a complete amelioration of the symptoms. The dose must be individualized.

Wilhelm (1961) has reviewed the therapeutic uses of the antihistaminic drugs and evaluated the relative advantages of the many members of this pharmacologic class.

**Choice of an antihistaminic.** With so many available compounds which antagonize the effects of histamine, it is not an easy matter for the clinician to select the best drug for his particular cases. The official antihistaminics appear to be favored by many allergists.

All of these drugs have been reported to provide good clinical responses in urticaria, rhinitis, and dermatitis associated with allergic states. Only the mildest cases of asthma are improved by these agents. The choice of a drug seems to be related to the incidence of side effects that it produces. As previously discussed, this is a matter that must be determined for each patient.

Chlorpheniramine is an effective antihistaminic with a low incidence of side effects. This drug is comparable in therapeutic efficacy to other antihistaminics although the average dose is only 2 to 4 mg. Triprolidine is perhaps the most potent antihistaminic with a low toxicity, rapid onset of action, and a prolonged effect. It is usually administered orally in 2.5 mg. doses. Unlike most antihistaminics which are bitter, triprolidine is virtually tasteless. Brompheniramine is another potent antihistaminic with a dose of 4 mg. Dexchlorpheniramine, which is the dextro isomer of chlorpheniramine, is used in 2-mg. doses, 3 or 4 times daily.

The favorable clinical reports on promethazine warrant special mention. Promethazine is very efficacious and long-acting. The best response is obtained in urticaria and angio-edema. The soporific effect of this drug is quite marked, and it has been found to be a good substitute for the barbiturates in certain patients. Promethazine in doses of 25 mg. administered orally at bedtime is the usual antihistaminic dose.

It appears that at present the various compounds available as histamine antagonists are effective when administered in therapeutic doses in about ⅔ of the cases of allergic conditions. Side effects are common to all of these drugs. With diphenhydramine and promethazine, drowsiness appears to be maximal, occurring in as many as 50 per cent of the patients. With the others, the incidence of drowsiness is well under 10 per cent.

More clinical experience has accumulated with diphenhydramine and tripelennamine. These drugs, in addition to chlorpheniramine and promethazine, warrant first consideration.

**Antihistaminics in the common cold.** Remedies used in the treatment of the common cold are very difficult to evaluate. There were several fragmentary reports of the value of diphenhydramine in the treatment of the common cold in the early days of its use. In 1949 there was a colossal resurgence of the use of many of the then new antihistaminics in the treatment of the common cold. Based upon the proposal that the early symptoms of the common cold are similar to those of histamine response, the antihistaminics were widely employed in this country. There is not general agreement, however, that colds can be treated as an allergy. Persons who are not sensitive to the proteins in the cold virus, may not experience the early symptoms of allergic response and will likely not benefit by the administration of the antihistaminics.

Certain of the antihistaminic drugs are sold without a prescription in doses of 10 to 25 mg. for the treatment of the symptoms of the common cold. In the years 1957–1958 an estimated 40 million people in the United States used these drugs with little or no medical supervision before the enthusiasm for their virtues waned. It is remarkable indeed that so few toxic effects resulted from their use in this manner.

In 1950 Feller *et al.* demonstrated that in carefully controlled experiments the antihistaminic drugs did not prevent or cure the common cold or other associated undifferentiated respiratory diseases. Their work was based upon the course of infection in volunteers inoculated with the cold virus. Other clinical trials were reported which failed to support the use of these drugs in the common cold.

The best that one can hope to achieve by dosing with the antihistaminics in the treatment of the common cold is that of amelioration of the symptoms. The cause remains unaffected, and the course of the disease appears not to be shortened. The use of the antihistaminics with other drugs such as aspirin, caffeine and acetophenetidin seems to be unwarranted.

**Untoward reactions produced by the antihistaminics.** The antihistaminic drugs cause a high incidence of side reactions. In most instances, however, these are of a minor character. *Sedation* and *drowsiness* appear to be the most common complaint. Some observers state that the incidence of undesirable reactions may be as high as 20 per cent. However, with continued therapy in most cases these minor complaints disappear. In some instances the degree of sedation may be so marked as to preclude normal activity. Indeed, some of these drugs have been employed to produce sleep in hospitalized patients requiring a hypnotic. For this purpose their use seems to offer little advantage over the barbiturates. In table 58-1 one may observe combinations of the antihistaminics with central stimulants, *e.g.*, ephedrine, in pharmaceutic dosage forms. Preparations of this character are designed to reduce the drowsiness experienced by the use of the antihistaminic drugs.

Other side reactions elicited by these drugs are nausea, headache, vertigo, xerostomia, restiveness, and occasionally gastrointestinal distress.

Dermatologic complications and skin eruptions in patients have followed the local application or oral administration of the antihistaminics. Some reports have placed the incidence of these allergic responses between 2 and 4 per cent. There may or may not be cross-sensitization to other antihistaminic drugs.

**Toxicology of the antihistaminics.** Because these drugs are administered for long time periods, patients under continuous treatment should be examined periodically. Although blood dyscrasias have rarely been reported, the possibility of such a response must not be overlooked.

Fatalities have followed the ingestion of large doses of the antihistaminic drugs. This seems to have been especially true in the case of small children. For example, death resulted in two 2-year-old children, one from 400 mg. of diphenhydramine hydrochloride and one from 1.3 gm. pyrilamine maleate, respectively (Lecks, 1951).

Overdosage causes *drowsiness* followed by *nervousness*, *tremors*, *muscle twitching*, *delirium*, and *convulsions*. Respiratory depression may be very marked with an accompanying cyanosis and fever. Unconsciousness may follow quickly or be delayed. Death has occurred following overdosage within 1 to 24 hours.

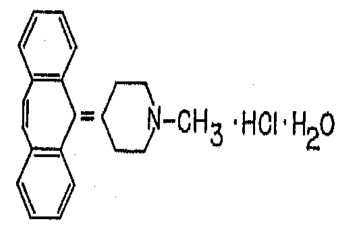
Treatment of acute poisoning with the antihistaminic drugs is difficult and has not been very successful. Respiratory stimulants may be helpful in the early stages of the depression but these may only tend to aggravate the onset of convulsive seizures. The convulsions can be combated by the use of intravenous thiopental sodium. Symptomatic treatment must be adapted to the individual. It is clear from the extensive experience that has been gained with these drugs that less toxic agents are needed.

### The Antiserotonin Drugs

Serotonin has been considered as a biologically significant amine in several sections of the text, *e.g.*, its role in hypertension and in the central nervous system. Serotonin captured the attention of allergists because in the carcinoid syndrome wheezing is a prominent symptom. This syndrome is characterized by a high serotonin blood level. In addition, there is evidence that serotonin is released during antigen-antibody reactions in laboratory animals, and relatively high serotonin blood levels have been found in allergic patients. There is an extensive literature on this subject (Grover, 1963).

Without our understanding the significance of serotonin and its relationship to the allergic diseases, drugs have been discovered that are effective therapeutically and antagonize the pharmacologic effects of serotonin in laboratory animals. These drugs are also antihistaminic agents.

**Cyproheptadine (Periactin).** This drug is the hydrochloride of 1-methyl-4-(5-dibenzo-[a,e]-cycloheptatrienylidene)-piperidine.



Cyproheptadine

Cyproheptadine hydrochloride is a serotonin and histamine antagonist recommended primarily for the treatment of pruritic dermatoses. Its antiserotonin actions include the inhibition of the vasopressor action of serotonin in the anesthestized, ganglionic blocked dog; inhibition of the spasmogenic effect of serotonin on the isolated rat uterus; and inhibition of rat paw edema produced by serotonin. Its antiserotonin actions in protecting mice against anaphylactic shock and death are significant (Stone *et al.*, 1961).

Cyproheptadine antagonizes the effects of histamine in a manner similar to other antihistaminic agents. It is a potent antihistaminic. The drug is effective in antagonizing histamine-induced gastric secretion. This latter action is more pronounced than other antihistaminic agents. Cyproheptadine possesses a number of pharmacologic effects apparently unrelated to its antiserotonin or antihistaminic actions (Stone *et al.*, 1961).

Cyproheptadine is used in the relief of pruritus associated with urticaria, angioneurotic edema, dermatitis, and those dermatoses caused by drugs, or contact with sensitizing agents. It is administered orally as tablets or as a syrup in doses of 4 to 20 mg. per day. Dosage must be individualized. Drowsiness, which may not be undesirable for some patients, is the most frequent side effect. Dry mouth, dizziness, nausea, and skin rash have been reported to occur in certain patients after administration of the drug.

**Methysergide Maleate (Sansert, UML-491).** Methysergide is 1-methyl lysergic acid butanolamine maleate. It is the most potent antiserotonin substance known. It has been found to be highly effective for the prophylactic treatment of headache and it is discussed in chapter 35 under lysergic acid derivatives. The drug is effective in histamine cephalgia, but its mechanism of action is not completely understood.

### Pharmacologic Agents in Bronchial Asthma

Much progress has been achieved in recent years in the symptomatic treatment of bronchial asthma. Since the introduction of corticosteroids, these hormonal drugs have assumed an important place in asthmatic therapy. As pointed out previously, the antihistaminic drugs may or may not be beneficial depending upon the implication of histamine in the syndrome of bronchial constriction. Their chief value to the asthmatic seems to be as a prophylactic to prevent the initial inciting cause of an asthmatic seizure. The antihistaminics are ineffective in treating the acute paroxysm of dyspnea of asthma. Autonomic drugs, especially the adrenergic agents, are most useful in the relief of the asthmatic spasm. In addition to the relaxation of the bronchial musculature caused by drugs which act through the autonomic innervation of the bronchial musculature, the xanthine alkaloids, which relax smooth muscle by their direct musculotropic action, have had wide use in asthma. In children and adults whose asthma has an infectious etiologic factor, gamma globulin injections have been reported as reducing the frequency of upper respiratory tract infections. If asthma is accompanied by hypogammaglobulinemia, these patients will receive dramatic relief of symptoms from gamma globulin administered intramuscularly every 2 or 3 weeks.

**Therapeutic use of bronchodilator drugs.** The sympathetic division of the autonomic nervous system innervates the bronchial musculature in a manner that is reciprocal to the vagus fibers. Upon sympathetic stimulation the bronchi dilate, and the tidal volume is increased. Epinephrine, and to a lesser degree norepinephrine, liberated at the effector cells in the bronchi are responsible for this effect. Atropine by virtue of its blocking action of acetylcholine prevents the bronchial constriction elicited by stimulation of the vagal fibers to the bronchi. Hence this alkaloid is used in asthma. The pharmacology of these drugs is discussed in chapters 34 and 37.

An important advantage which the sympathomimetic amines offer over the cholinergic blocking agents such as atropine is that they do not cause the drying and plugging of mucus in the bronchioles. This stems from the fact that atropine not only blocks the motor component of the action of acetylcholine but also its secretory activity.

The problem of epinephrine fastness occasionally encountered in patients may be due to the release of histamine from the tissues of the host. Indeed it is often successfully obliterated by the administration of one of the antihistaminics. Sodium lactate solution intravenously may be effective to combat epinephrine fastness, page 544.

The sympathomimetic amines which are prominently employed in asthma are epinephrine, isoproterenol, phenylephrine, and ephedrine. The isoproterenol (Isuprel) linguet is very popular. Isoproterenol does not elevate the blood pressure, nor does it impose an additional work load on the heart without concomitant coronary dilatation as does epinephrine. Besides, it does not elicit hyperglycemia, as is evoked by epinephrine.

Aerosols of sympathomimetic drugs are now available in convenient pocket units. The solution is converted to an aerosol by a Freon propellant. These devices are designed to deliver measured aerosol dosages. Epinephrine and isoproterenol are available in units called Medihalers. Aerosols of 2.25 per cent racemic epinephrine (Vaponefrin) hydrochloride, and isoproterenol (Aludrine, Isuprel) hydrochloride in 1:200 concentration have proved to be of value in the treatment of bronchospasm.

Dextro-pseudoephedrine (Sudafed) is a stereoisomer of ephedrine which produces a decongestive and bronchodilator effect when administered orally in 60-mg. doses, 3 to 4 times a day. Ephedrine salts may be combined with antihistaminic agents. These drugs administered by mouth will exert their effect for several hours and may have prophylactic value.

Theophylline is the most potent xanthine base from the standpoint of its smooth muscle relaxing properties and the vasodilatation which it produces. Aminophylline is theophylline solubilized by combination with ethylenediamine. Without the latter, theophylline is capriciously absorbed from the gastrointestinal tract. If the stomach is rich in acid, aminophylline may be decomposed into its component molecules, and absorption thereby diminished. The drug is absorbed fairly uniformly from rectal suppositories. However, if given in a high enema the absorption is prompt and the blood level is tantamount to that achieved by an intravenous injection, namely, 0.5 mg. per cent. When aminophylline is used for maintenance therapy in asthma, it appears that its principal function is that of bronchiolar dilatation with a minimal effect upon the edema of the bronchioles. One of the problems in aminophylline therapy is to achieve adequate dosage levels without gastric irritation. This may be accomplished partially at least by the use of the less irritating theophylline sodium glycinate or by the use of enteric coated aminophylline tablets.

Aminophylline 0.5 gm. intravenously in status asthmaticus should be employed with special caution as there have been so many misadventures in therapeutics with this important restorative measure. Rapid injections of aminophylline may through central vagal stimulation cause profound bradycardia or even cardiac stoppage. Slow injections, well diluted with salt solution, are safe and provide electrolytes and fluid to the patient.

**Adrenocortical steroids.** Many cases of status asthmaticus refractory to the usual measures of therapy have yielded dramatically to treatment with either corticotropin or cortisone. While these agents are not the drugs of choice because of their objectionable side actions, in many chronic and acute cases they are exceedingly useful.

ACTH owes its value to its stimulating effect upon the adrenal cortex from which it induces the secretion of the adrenal steroids. Unfortunately, it is not available for oral administration as are the corticosteroids. The long-term treatment of asthma with cortisone involves the risks of sodium retention, hypertension, peptic ulcer exacerbation, and calcium loss from the osseous structures. Fortunately, the availability of Prednisone has substantially reduced most of these hazards. This agent is 4 to 5 times more potent than cortisone, and patients may be maintained at daily dosage levels of 7.5 mg. without appreciable disturbance of electrolyte balance or other untoward side effects. With this smaller dose complications of therapy such as fluid retention are less likely to occur. Prednisolone is administered in the same doses as Prednisone. Methylprednisolone and Triamcinolone in general are employed in doses approximately ⅔ the required daily dose of Prednisolone or Prednisone. The dose of Dexamethasone is still smaller; approximately 0.75-mg. oral doses are equivalent to the anti-inflammatory effects of 25 mg. of cortisone (Pinkerton and Van Metre, 1958).

The mechanism by which the corticosteroids promote the relief of asthma is not clearly understood. Certain facts, however, are suggestive. These steroids serve to restore to normalcy diffusion through the capillary membranes. As loss of fluid and electrolyte through the impaired capillaries in the bronchi is a source of the edematous swelling, this effect may be of marked importance in the beneficial action which they mediate. Further, the steroids stimulate tissue metabolism and cause gluconeogenesis through protein destruction. It is possible that this action might involve the destruction of the protein portion of the allergotoxin molecule. Additional studies are necessary to elucidate more adequately the action of these steroids in asthma. The pharmacology and dosage schedule of the adrenocortical steroids are given in Chapter 53.

**Expectorants in bronchial asthma.** The therapy designed to dislodge, reduce in viscosity, and expel mucus has changed little over the years. Iodides remain as useful drugs. The iodide ion is effective in the dissolution of mucus. But the problem in therapy is to bring the iodide ion in sufficient concentration to the impacted bronchioles. Intravenous therapy appears to offer little advantage over oral administration.

When iodides are given in quantities of 1 to 3 gm. daily, iodide can be demonstrated in the bronchial secretion. Whether or not it is there in sufficient quantity to cause the dissolution of mucus has not been established. It is clear, however, that if iodides are impinged upon the gastric mucosa of a cat, the bronchial secretion is increased 4 to 5 fold. This action is reflex in character, for it is abolished by severance of the vagus nerve. Ipecac and ammonium chloride cause increased secretion in the bronchioles in the same manner. That this reflex action is a primitive one is shown by the fact that it is not abolished by light anesthesia. This poses the challenging clinical question of the wisdom of protecting the gastric mucosa from the irritating action of the iodide ion. Potassium iodide is usually given by mouth in 0.5 to 1 gm. doses 3 times a day and the dose increased to the limit of gastrointestinal tolerance. Presumably some degree of irritation of the gastric mucosa is necessary for the reflex bronchial stimulation of secretions by potassium iodide.

Antitussive therapy with a combination of diphenhydramine hydrochloride and aminophylline (Hydryllin), or carbetapentane citrate (Toclase) in an expectorant base may be useful to control a troublesome bronchial cough and prevent the triggering of a bronchiolar spasm.

The expectorants ammonium chloride and syrup of ipecac still enjoy a wide use in asthma therapy. This is certainly not because of their efficacy or dependability, but owing to the fact that better agents are not available.

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# *Supplemental Therapeutic Aids*

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Consideration is given in this part of the text to those substances that are used as therapeutic supportive measures. Most of these agents are not drugs *per se* but because of their mechanical, chemical, or physiologic effects they enhance drug action. These substances are classified as *supplemental therapeutic agents*. Those preparations employed as medical or surgical aids as adjuncts to specific drugs, enzymic products for debridement of necrotic tissue, and topical applications of chlorophyll derivatives are discussed. The cation exchange resins currently of interest in the management of edematous states are included. In recent years blood substitutes have been the subject of intensive study. A brief resume of the various plasma substitutes is presented in this section of the text.

## Drugs Used in the Treatment of Wounds

### Enzyme preparations.

**Laboratory evaluation of enzyme debridement.** The use of enzyme preparations in the treatment of wounds containing accumulations of necrotic tissue is now widely practiced. Laboratory methods for the evaluation of new agents are not satisfactory. Recently Douglas *et al.* (1958) described a technic to screen debriding agents *in vivo* in the guinea pig. A controlled skin burn is produced in an anesthesized animal which produces an eschar suitable for treating within one week. The debriding agent is applied in a water-soluble jelly base for 3 days with an estimation of the degree of tissue digestion. Comparative results can be obtained by this method that will permit an assessment of the relative merits of an enzyme preparation. An *in vitro* method is also employed which uses a spun-collagen fiber. A 40-filament thread is used, and the time required for the fiber to break under a 2-gm. weight load as influenced by the action of the protease enzyme is recorded.

**Trypsin Crystallized, N.F. (Parenzyme, Tryptar).** Crystalline trypsin derived from mammalian pancreas is soluble in a phosphate buffer solution. This solution, which exerts proteolytic activity between pH 5 and 8, is prepared fresh for use for debridement of surfaces covered with necrotic tissue and pyogenic membranes. The enzyme does not attack healthy cells or connective tissue collagen. The dry powder may also be used. Trypsin solution is not bactericidal, but it seems to encourage normal healing by denying a favorable medium for invading bacteria.

Crystallized trypsin is assayed by its ability to digest the substrate, N-benzoyl-*l*-arginine ethyl ester hydrochloride. Its activity is compared to a reference standard. The National Formulary requirement for trypsin is not less than 2,500 units/mg. The substance is a white, crystalline or amorphous powder, stable indefinitely in the dry form at room temperature. In sodium chloride solution or water, 80 per cent of its proteolytic activity is retained for 72 hours.

The therapeutic use is based upon selective enzymic digestion of nonviable cells and tissues. Its action is rapid, and external surfaces of burns and comminuted fractures may be cleaned in a few hours. Trypsin preparations are useful as an adjunct to the surgical debridement of necrotic wounds, ulcers, abscesses, and to assist in the separation of the eschar of second degree burns.

A trypsin preparation is employed in enzymic debridement of indolent, infected cutaneous ulcers. The purified dry powder or a wet dressing is applied to the surface of the ulcer. Extensive studies have indicated that the enzyme causes the complete digestion of fibrin, clotted blood, pus, and necrotic tissue. It does not affect the normal blood supply to the necrotic area. Healing progresses at an accelerated rate because the removal of cellular debris permits a more effective action of antibiotic agents.

Trypsin will liquefy hematomas and coagulated blood and exudates. For this reason the enzyme has been used in a number of disease states associated with blood stasis and clotting.

*Parenteral administration of trypsin.* Based upon the observation that intravenous administration of trypsin solution produced fibrinolysis in animal experiments, trypsin was employed intravenously in patients with acute inflammatory reactions, *e.g., thrombophlebitis, thromboangiitis obliterans, coronary occlusion*, and *acute rheumatoid arthritis.* Clinically the results were favorable. In many instances there was a dramatic subsidence of acute inflammation.

Subsequent investigations have demonstrated that intramuscular injections of trypsin in oil were more satisfactory. A sesame oil solution of trypsin containing 5 mg./ml. has been used. The usual dose is from 2.5 to 5 mg. 1 to 4 times daily for a period of 3 to 8 days. Many patients have responded favorably to this treatment when the drug was injected by deep intragluteal administration. Patients refractory to customary therapy in thrombophlebitis may obtain beneficial results. Anticoagulant therapy should not be omitted, and trypsin therapy is to be considered adjunctive. Controlled studies on the use of trypsin in these difficult to evaluate clinical states have not been reported. It may be assumed that the preparation is useful. Trypsin is not as potent a fibrinolytic agent as streptokinase. The drug is more effective in the liquefaction of coagulated blood and exudates than it is in the removal of necrotic tissue (Glass and Fischer, 1959).

Intravenous or intramuscular therapy with trypsin should not be employed in cases of hepatic insufficiency, hemorrhagic states, severe anoxia or cachexia, or in patients with congestive heart failure. The possibility of a hypersensitivity reaction should not be overlooked, and a test should be made before the start of a second series of trypsin injections.

Trypsin is applied as a wet dressing or by irrigation as a solution containing 10,000 units

of the crystalline enzyme per ml. of physiologic sodium chloride solution. The dry powder is applied as a thick coating and allowed to remain intact for not more than 3 hours.

*Nebulized trypsin in respiratory diseases.* An aerosol of a trypsin solution has been used in bronchial asthma, bronchiectasis, and respiratory conditions associated with dyspnea and a viscous sputum. A solution containing from 40,000 to 50,000 units of trypsin (Tryptar aerosol) in 1 ml. in a Sörensen's phosphate buffer to maintain the proper pH is nebulized with oxygen. Inhalations of 1 ml. aerosolized 3 to 6 times daily are repeated for 3 to 7 days. This therapeutic regimen has been employed with patients who proved unresponsive to the usual expectorants and bronchodilators. The greatest benefit was obtained by patients with a thick, copious sputum. A change in the fluidity of the sputa of patients is associated with a decrease in dyspnea, wheezing, and râles. Not all cases are benefited, and mild local irritation is experienced by some individuals after the aerosol inhalations. Intramuscular injections of aqueous solutions or oil suspensions of crystalline trypsin are more likely to give satisfactory results in severe bronchopulmonary diseases. The effectiveness of trypsin in bronchopulmonary disease has not been demonstrated to be completely satisfactory; other agents appear to be superior.

**Streptokinase and streptodornase (Varidase).** The elaboration of a substance which causes fibrinolysis by a growing broth culture of hemolytic streptococci was discovered in 1933 by Tillett and Garner. The active principle has been purified and concentrated and found to be an enzyme and an enzyme activator. This material, called streptokinase, is derived from bacterial organisms nonpathogenic for man. Streptokinase is an enzyme which serves to activate plasminogen in human serum; an active fibrin lysing results which is capable of rapidly dissolving blood clots *in vitro.*

Tillet *et al.* (1948) showed that the desoxyribose nucleoprotein formed in pus imparts a stringy, slimy, viscous, coarsely-particulated appearance to pus and purulent exudates. An enzyme which causes liquefaction of this complex protein is called streptodornase. Like streptokinase, it is elaborated simultaneously in the growth phase of individual strains of hemolytic streptococci. The activity of both enzymes is characterized by the process of liquefaction of viscous, gel-like tissue substances.

Streptodornase is a deoxyribonuclease, or a mixture of closely related enzymes, capable of splitting nucleoprotein into free purine bases and pyrimidine nucleosides. This action causes the reduction in viscosity of purulent material.

Streptokinase is an enzyme activator that changes the serum factor plasminogen into an active enzyme plasmin which causes the fibrinolysis of the blood clot. This enzyme activator may explain the eventual liquefaction of cadaver blood.

A preparation of the lyophilized, partially purified, bacteria-free filtrate of culture media of group C hemolytic streptococci containing streptokinase and streptodornase is available. This product is known as Varidase. The enzymes are standardized on the basis of units: 1 streptokinase unit is defined as the activity contained in an amount of solution which will cause lysis of a standard fibrin clot in 10 minutes when compared with a standard preparation; 1 streptodornase unit is the amount of enzyme which will cause a change in the relative viscosity from 5.0 to 4.0 of a 0.15 per cent solution of deoxyribonucleic acid in 10 minutes at 30°C.

Streptokinase-streptodornase has no effect on living cells, and a solution of the preparation may be injected directly into a body cavity or applied locally. *It is not injected intravenously.* This preparation has been used in surgery and skin grafting for the removal of dead tissue and to hasten tissue regrowth. Effective combined local therapy with antibiotics is most desirable. Streptokinase-streptodornase has been used in the treatment of hemothorax, empyema, osteomyelitis, draining sinuses and tuberculous abscess, severe burns, chronic suppurations, and hematoma.

The commercially available Varidase consists of a mixture of 100,000 units of streptokinase and 25,000 units of streptodornase in 1 ampule. The dry powder is dissolved in 20 ml. of sterile saline immediately before use. This solution is for topical use. The parenteral dosage is related to the amount of coagulum or purulent exudate present and may vary from 1,000 to 200,000 units of streptokinase with from 250 to 50,000 units of streptodornase. A powder for injection is available containing 20,000 units of streptokinase and 5,000 units of streptodornase. A jelly for topical use is available containing 100,000 units of streptokinase and 25,000 units of streptodornase. The solutions will deteriorate in potency at room temperature. They may be preserved for one week at 2° to 10°C. Aseptic precautions are necessary to avoid contamination of the solution or jelly.

*Intramuscular use of streptokinase-streptodornase.* The intramuscular use of streptokinase-streptodornase in dosages of 5000 units of streptokinase twice daily has been suggested in the treatment of edema associated with infection and trauma. Edema fluid present in such lesions usually contains a high amount of fibrin. Such high fibrin concentrations are likely related to the natural defense mechanism of the tissues, since the coagulation of this substance helps to wall off the damaged area. This entire sequential process has been recognized traditionally as the "defense curtain" in that it localizes and restricts the damaged area and inhibits the spread of infection. Surgically, the dictum of noninterference with this "limiting membrane" has been a basic consideration. With the availability of antibiotics it became clear that tissue penetration of these agents from the blood to the abscesses, walled off cellulitis, or similar infected and restricted areas was inhibited. By using these lytic enzymes intramuscularly these "limiting membranes" could be penetrated, and antibiotics administered concomitantly would be rapidly effective in clearing the infection.

Streptokinase-streptodornase may be administered by the buccal route in the form of tablets containing 10,000 units of streptokinase and 2,500 units of streptodornase. The tablet is placed in the buccal pouch or under the tongue and allowed to dissolve slowly. This dose is repeated 4 times daily. This avenue of administration is equivalent to intramuscular injection in the management of inflammatory edema.

Untoward reactions to streptokinase-streptodornase therapy are minimal if careful attention is directed to the removal of exudates and liquefied debris from closed areas. Pyrogenic reactions are the most common untoward effect. Allergic reactions have been reported rarely, but care must be exercised to avoid these effects. Temperature elevation and an anaphylactoid-like response may occur most often in patients with massive extravasations of blood. These systemic reactions are rarely seen in the treatment of superficial suppurations or freely draining areas.

It appears that this enzyme preparation is a very useful supplemental therapeutic agent. As an effective "physiologic curette" the drug supplement permits more effective chemotherapeutic control of both superficial and deep tissue infections. The only serious limitation in the use of streptokinase-streptodornase is a poor blood supply to the involved area. Gangrene is a definite contraindication. Cellular destruction may occur as a result of the digesting action of the enzymes on those cells that may be of marginal viability, *e.g.*, after irrigation.

Streptokinase-streptodornase are perhaps most useful when applied by injection into cavities and when used topically in wet dressings to keep the enzymes in contact with the tissue substrate. For hemothorax, to remove clotted blood or fibrous, purulent accumulations, the enzyme preparation is an aid to normal tissue repair and healing. These agents are supplements to surgical debridement.

**Fibrinolysin-human (Actase), Thrombolysin.** Human fibrinolysin is prepared by the action of streptokinase on profibrinolysin isolated from human plasma. It is not known whether residual streptokinase remains in the preparation and hence may influence its effects as a fibrinolytic agent.

Human fibrinolysin causes the breakdown of fibrin into incoagulable substances *in vitro*. The end-products are probably large polypeptides. *In vivo* an inactive precursor of fibrinolysin is known to be present in human blood.

Human fibrinolysin is administered intravenously in various forms of thromboembolic disease. As an adjunct to the management of phlebothrombosis, pulmonary embolism, and thrombophlebitis the preparation is effective. It is considered to be potentially useful in the treatment of thrombosis or embolism of the cerebral or coronary circulation, but its place in this form of therapy remains to be established.

Toxic reactions and untoward effects that have followed the use of human fibrinolysin are epigastric pain, febrile reactions, nausea, vomiting, and electrocardiographic changes. Urticarial rashes and serum sickness have been produced by this preparation. The material must be considered a potentially potent antigen and due care must be exercised in its use, especially upon repeated administration.

There is no adequate standardization of these products and the optimal dosage has not been established. The activator potency of the preparations is many times their fibrinolysis content that is measured in "fibrinolysin units". The unit has been defined separately by manufacturers and investigators. No two units are equivalent; 1 unit may represent 5, 10, or 20 times as much activity as another. Physicians must know the potency and limitations of these preparations if they use them in therapy.

**Pancreatic Dornase (Dornavac).** This product is the stabilized enzyme deoxyribonuclease prepared by the fractional precipitation of aqueous acid extracts of beef pancreas. Dornavac for inhalation is a lyophilized preparation, 100,000 units per vial. The activity is measured by determining the rate of reduction of viscosity of thymus deoxyribonucleic acid; 1 unit is the amount of enzyme that causes a reduction of 1 viscosity unit in 10 min. at 30°C.

This enzyme is a single nuclease. Its substrate is deoxyribonucleoprotein, unlike streptodornase, which is a mixture of a related group of enzymes. The chief difference between these 2 preparations is the degree of depolymerization of deoxyribonucleoprotein. Pancreatic dornase rapidly depolymerizes the deoxyribonucleoprotein to relatively large molecular fragments. Streptodornase continues the depolymerization and degradation to free purine and pyrimidine derivatives.

Pancreatic dornase acts upon extracellular secretions and not upon viable cells. It is used to reduce the viscosity of thick secretions in bronchopulmonary infections and to facilitate the expectoration of sputum and enhance the degree of pulmonary ventilation in bronchiectasis, abscesses, emphysema, chronic bronchial asthma, and the respiratory complications of cystic fibrosis.

Pancreatic dornase is administered by inhalation as an aerosol. For bronchopulmonary infections the dosage ranges from 50,000 to 100,000 units 1 to 4 times daily for a period of one to 7 days. The solution is prepared in sterile isotonic solution of sodium chloride immediately prior to use. The toxicity of the enzyme appears to be low, and allergic reactions have not been serious following the use of the drug.

**Fibrinolysin and desoxyribonuclease (Elase).** This preparation contains fibrinolysin of bovine origin and deoxyribonuclease. The fibrinolysin is said to be active (plasmin) and hence does not need an agent to activate the profibrinolysin in exudates. The product is to be used only by topical application. It is proposed that the preparation be employed to lyse fibrin and liquefy pus; it is said to be effective in the removal of necrotic debris and exudate from skin surfaces in wounds, ulcers, and burns. The preparation is available in vials of 25 units of fibrinolysin and 15,000 units of desoxyribonuclease for the preparation of a solution.

**Chymotrypsin (Alpha-Chymar, Avazyme, Chymar, Chymotest, Enzeon).** Chymotrypsin, also known as alpha-chymotrypsin, is obtained in crystalline form from mammalian pancreas by aqueous acid extraction of its proenzyme, chymotrypsinogen, and its subsequent conversion with trypsin to chymotrypsin. Preparations are available for intramuscular injection: 5,000 units/ml. in sodium chloride solution, a suspension in oil of 5,000 units/ml. for intramuscular injection, and a buccal tablet containing 10,000 units per tablet.

Chymotrypsin is proposed for use in reducing inflammation of all types. It is used to reduce edema and hematomas and to improve local circulation and reduce the pain in thrombophlebitis, cellulitis, burns, bruises, ulceration, and fractures. The enzyme acts as a proteolytic agent.

Chymotrypsin has been incriminated as the agent responsible for anaphylactic shock and hypersensitivity reactions when it was used in the relief of painful episiotomy wounds. Adequate hypersensitivity testing must be carried out before agents of this type are employed.

Alpha-Chymar is crystallized alpha-chymotrypsin used in the treatment of cataract to break down the zonule fibers of the lens and to reduce trauma of the eye tissues. The use of the enzyme may permit a more satisfactory removal of cataract opacity of the lens.

A number of pharmaceutical preparations are available containing trypsin, chymotrypsin, and ribonuclease and related enzymes. The physician should employ these preparations with great caution. The undesirable side effects that they may produce in some patients can be serious.

**Hyaluronidase, U.S.P. (Wydase, Alidase, Diffusin, Hyazyme).** Hyaluronidase is an enzyme identified by its specific action on its substrate, hyaluronic acid. Because of its action in breaking down hyaluronic acid, the enzyme is useful in promoting the diffusion of solutions injected hypodermically. Thus hyaluronidase is used in hypodermoclysis, local anesthesia, in urography to speed the absorption of radiopaque dye, and in certain other clinical conditions where it is desirable to increase the tissue penetration of injected fluid.

In order to understand the mechanism of action of hyaluronidase, a brief description of hyaluronic acid is necessary. Hyaluronic acid is a mucopolysaccharide acid found in many animal tissues. This material is a gel in the *ground substance* in connective tissue that acts as a barrier to fluid diffusion. It has been described as a tissue cement and apparently plays a role in the formation of collagen. It also serves as a lubricant and shock-absorber in joints. Capillary permeability has been increased in experimental animals by intravenous injection of large doses of hyaluronidase, indicating that hyaluronic acid is present in capillary cement substance, or at least in the connective tissue bed of capillaries. Clinically, however, hyaluronidase is not employed when injections are made into body cavities or blood vessels.

The chemical structure of hyaluronic acid is imperfectly known. Hyaluronidase is an enzyme and therefore possesses protein characteristics. Pure hyaluronidase has a molecular weight of approximately 60,000. The enzyme can be identified and isolated from a number of sources—bacterial cultures, leeches, snake venoms, and animal tissues. The hyaluronidase used clinically is derived chiefly from bovine testes. The enzyme preparation is standardized on the basis of viscosity reduction units or turbidity reduction units. These units are based upon the amount of enzyme required to reduce the viscosity or turbidity of a standard hyaluronate substrate. A review of the nature and properties of hyaluronidase is given in the New York Academy of Sciences symposium (1950).

*Hyaluronidase for Injection, U.S.P.*, is standardized by measuring the depolymerizing effect of hyaluronidase on hyaluronic acid. The action of the enzyme is associated with a reduction in turbidity. Commercial preparations available contain 150 and 1500 U.S.P. hyaluronidase units.

Hyaluronidase is supplied in a dried, lyophilized form. The solution deteriorates on standing. For clinical use a freshly prepared solution is employed containing 150 U.S.P. units/ml. of isotonic sodium chloride. One ml. of this solution is added to each 1000 ml. of solution for hypodermoclysis. This same amount of the enzyme may be added to 50 ml. of solution containing 0.5 ml. of epinephrine hydrochloride 1:1000 for subcutaneous, intracutaneous, or intramuscular injection for nerve block anesthesia.

Hyaluronidase may be used in combination with heparin for intramuscular injection. The disadvantages of pain and local bruising associated with heparin injections are overcome by the use of 0.1 mg. of hyaluronidase powder per 150 mg. of heparin.

Several precautions must be observed when hyaluronidase is used. Hypersensitivity to the enzyme may occur. It can be discovered by a skin or conjunctival test before injection. Hyaluronidase is apparently quite nontoxic, according to the experimental trials in animals. Because hyaluronidase encourages penetration of tissue fluids, it should not be injected into an area where there is local infection. To do so may enhance the spread of the infection.

**Papase.** This is a proteolytic enzyme mixture extracted from *Carica papaya*. It is said to be effective in reducing experimentally-induced hematomas in human volunteers and to have anti-inflammatory effects in animals. The product is available as tablets, 10,000 units per tablet, to be administered buccally or chewed and swallowed. The effectiveness of the agent remains to be established by clinical experience. Toxic reactions produced by papase have not been reported.

### Chlorophyll deodorizer

A number of forms of chlorophyll are known, and the chemistry of this pigment has been studied extensively. Chlorophyll "a" and "b" are magnesium porphyrin complexes insoluble in water but soluble in fat solvents. These forms may be converted to water-soluble sodium magnesium chlorophyll by alkaline hydrolysis. Commerical chlorophyll preparations contain both "a" and "b" forms of water-soluble chlorophyllins. The magnesium of the chlorophyllin can be replaced by copper, iron, nickel, or other metals. The type of metal introduced into the molecule determines the use of the chlorophyllin. Generally the salts of copper or magnesium chlorophyllins are used in pharmaceutical preparations.

The structural similarity of chlorophyll and hemin in hemoglobin is of considerable theoretical interest. The chlorophyll magnesium complex resembles hemoglobin in that Mg is substituted for Fe and the phytol radical replaces globin. Thus the structures of both hemoglobin and

chlorophyll resemble in a striking manner the chelating structure of some recently discovered antibiotics of which erythromycin is an outstanding example. The anti-bacterial virtues of chlorophyll may be related to this chemical property.

**Chloresium.** This preparation is composed of the water-soluble derivatives of chlorophyll consisting chiefly of the copper complex of the sodium and/or potassium salts of saponified chlorophyll. It is used clinically as a 0.2 per cent solution or a 0.5 per cent ointment.

Chlorophyll preparations are used for deodorization of chronic infected wounds and for the relief of itching in wounds, ulcers, burns, and dermatoses. These preparations have been administered by mouth to eliminate fecal odor in persons with a colostomy. In some cases very gratifying results were obtained. Chlorophyll is only mildly disinfectant. Some reports attribute to chlorophyll a stimulation of tissue metabolism and a subsequent stimulation of granulation and epithelization. The mechanism of action of its deodorant and epithelization effect is not clearly understood.

A number of reports in the literature have described beneficial results following the use of water-soluble chlorophyll preparations in the treatment of wounds, decubitus ulcers, and burns. Convincing evidence is lacking that these preparations are beneficial. The lack of toxicity of chlorophyll preparations is striking.

### ION EXCHANGE RESINS

The ion exchange resins used medicinally are polymers of high molecular weight synthetic resins. These substances in the form of a very fine powder are capable of transferring ions to and from the interface of the molecule. Cation exchange resins have a positively charged ion available for transfer, while anion exchange resins are negatively charged. These resins were used first medically to control the acidity of the gastric juice. Their use for this purpose is considered in the chapter dealing with gastric antacids. In recent years cation exchange resins were introduced in the treatment of edematous states where the body retains too much sodium. Thus these agents are employed along with diuretics and restricted salt diets in the management of congestive heart failure, edema, ascites, and hypertensive states.

When a cation exchange resin is ingested, it reaches the acid medium of the stomach, which contains $H^+$ and $Cl^-$ ions. The resin, usually an ammoniated substance, releases $NH_4^+$ ions into the stomach and adsorbs $H^+$ ions. It then reaches the intestine with $H^+$ ions available for transfer. In the alkaline medium of the intestine, where the resin is surrounded by $Na^+$, $K^+$, $HCO_3^-$, and $OH^-$ ions, another cation exchange takes place. $Na^+$ and $K^+$ ions are adsorbed by the resin, and in turn $H^+$ ions are released into the intestine:

$$[H^+][\text{Resin}^-] + [Na^+][HCO_3^-] \rightarrow$$

$$[Na^+][\text{Resin}^-] + [H_2CO_3]$$

The resin-bound sodium and potassium are excreted in the feces. The carboxylic cation exchange resins are used to precipitate the copper in the diet of patients treated for Wilson's disease.

**Carbacrylamine resins (Carbo-Resin).** One of the chief difficulties associated with the use of cation exchange resins is the tissue potassium loss. An attempt has been made to overcome this by using a carboxylic-type resin, 80 per cent in the hydrogen cycle and 20 per cent in the potassium cycle. In the stomach the $K^+$ ions are exchanged for $H^+$ ions. In the intestine the resin picks up $Na^+$ and $K^+$ ions in the approximate ratio of 4 to 1. Thus the potassium balance is not upset, since the resin has already prepaid the potassium debt.

If the patient can successfully use a low sodium diet, there is no need for resin therapy. However, the use of these resins does permit a moderate amount of dietary sodium and hence a more palatable diet.

**Kayexalate** is a sodium polystyrene sulfonate cation exchange resin. It is a golden brown, finely ground powder prepared in the sodium phase with an exchange capacity of approximately 3.1 mEq. of potassium per gm. The sulfonic form of resin is more rapid in action than the carboxylic-type, according to some views. This resin is prepared in the sodium phase for the purpose of removing excess potassium from the body. It has proved beneficial when given as an enema when it could not be administered orally. It has been used for the treatment of hyperkalemia in oliguria or anuria following acute tubular necrosis resulting from lower nephron nephrosis, hemoglobinuric nephrosis, "shock kidney," and "crush kidney." The average adult dose is 15 gm., 1 to 4 times daily.

**Dose of cation exchange resins.** A large total dose of 40 to 45 gm. of carbacrylamine resins per day is required. This is divided into 3 portions and taken at mealtime. The resin is mixed with water, fruit juice, or semi-solid food. Higher dosage does not remove appreciably more sodium, and less does not provide sufficient sodium control. A serious problem may arise from the daily ingestion of such a bulky powder. The patient experiences a sensation of something hot and acid in the mouth and esophagus when the material is swallowed. Again, as the substance leaves the stomach and enters the duodenum and begins exchanging hydrogen for sodium, the patient may complain of a warm, uncomfortable feeling. The chalky, unpleasant taste of the resin is sufficiently disagreeable to make this type of therapy impossible for some patients. Perhaps the most serious secondary effect resulting from the use of the cation exchange resins is *hyponatremia.* This is a condition where sodium concentration is depressed beyond that of chloride. Such a condition may arise from over-enthusiastic use of the ion exchange resins with a low salt diet.

Serious potassium deficiency may occur with the use of Kayexalate; thus it is imperative to determine the daily serum potassium levels. If this resin therapy is used intensively for more than a 3-day period, the serum calcium level should also be determined.

## BLOOD AND PLASMA SUBSTITUTES

There is need for a blood plasma substitute that would be available in combating shock in the multitude of casualties that would result from a major atomic military disaster. There is no complete substitute for whole blood in treating shock, but inasmuch as blood cannot be stored for indefinite periods of time, some substitute is needed. Although the search for plasma substitutes has engaged the attention of numerous investigators, no product has been developed that is entirely satisfactory.

A complete substitute for plasma would have all the attributes of plasma itself. It must have the proper osmotic pressure effect, it must remain in the circulation for a number of hours, it must be metabolized or excreted without toxic effects, it must not be antigenic, and it must be compatible with the elements of blood. Many substances have been tried or are undergoing study as plasma substitutes. Of these, dextran, gelatin, plasma protein fraction (human), and polyvinylpyrrolidone (PVP) appear to be the most promising.

**Blood.** The cell-free fluid portion of uncoagulated blood is *plasma.* When blood is allowed to coagulate and the cellular elements are removed, the fluid portion that remains is called *serum.* Plasma contains the proteins albumin, globulin, and fibrinogen. The fibrinogen is removed during the process of coagulation, and hence serum lacks this protein. Blood serum and plasma contain fats, inorganic and organic salts, immune bodies, and other soluble elements, in addition to the proteins described.

Blood serum and plasma may be prepared as a lyophilized, sterile, dry powder. This dry powder may be preserved and reconstituted by the addition of sterile, pyrogen-free water. The U. S. Pharmacopeia recognizes Citrated Whole Human Blood and Human Blood Cells. Whole blood for transfusion must be refrigerated at a temperature between 4° and 10°C, and it may not be used after 21 days of storage. Human Blood Cells are designated as "packed red blood cells." They consist of the cells separated from citrated whole human blood that is identified as to the donor's blood group and Rh type. The preparation may not be stored longer than 24 hours at a temperature not exceeding 10°C.

**Normal Human Serum Albumin, U.S.P.** This product is a sterile solution of the serum albumin component of blood from healthy donors. Normal human serum albumin is a moderately viscous, clear, brownish liquid. It is available as a 20-ml. injection containing 5 gm. of albumin, therapeutically equivalent to approximately 100 ml. of citrated plasma, and multiples thereof. Normal human serum albumin in a low volume dosage and high concentration provides effective treatment for shock, hypoproteinemia, and edema resulting from renal disease.

**Radio-iodinated Serum Albumin, U.S.P.,** is a sterile, buffered, isotonic solution containing radio-iodinated normal human serum albumin adjusted to provide 0.3 to 0.7 mc./ml. It is used as a diagnostic aid in blood volume and cardiac output determinations. Special radiation-testing facilities must be available for its use.

**Normal Human Plasma, U.S.P.** Normal human plasma is the sterile plasma obtained by pooling approximately usual amounts of the liquid portion of citrated whole blood from 8 or more adult humans who, at the time of the drawing of the blood, are free from any disease which is transmissible by blood transfusion. The U. S. Pharmacopeia describes the specific conditions under which the blood is collected. Normal human plasma may be dispensed as liquid, frozen, or dried plasma.

Freshly collected citrated human plasma is a slightly opalescent liquid of a faint yellowish or amber color. Normal human plasma is employed in the treatment of shock to combat hypoproteinemia when plasma is lost in severe burns, and as a temporary substitute for whole blood for the treatment of severe hemorrhage.

**Plasma protein fraction-human (Plasmanate).** This product is a plasma expander composed of 88 per cent albumin, 7 per cent alpha-globulin, and 5 per cent beta-globulin. The preparation is made from by-products obtained during the Cohn fractionation of human serum, in the process of recovering gamma-globulin and fibrinogen. The plasma substitute is used as a 5 per cent solution in a diluent of 0.75 per cent saline at a pH of 6.75 to 7.25. The osmotic activity is comparable to plasma. The solution is virtually potassium-free and made *hypotonic* electrolytically to avoid imposing a renal burden when it is injected.

The attributes of this plasma expander are its immediate availability as a clear, free-flowing, stable solution, its freedom from infectious agents, pyrogens, toxins, and antigens, and its low electrolyte level. The preparation is composed of physiologic protein material and for this reason may be superior to more artificial plasma substitutes.

Cock *et al.* (1958) used plasma protein fraction-human in the treatment of infants and children in acute shock states for the correction of hypoproteinemia. The acidosis, dehydration, and electrolyte depletion were corrected with satisfactory clinical improvement. In acute shock, as a plasma expander, 30 ml./kg. were infused intravenously up to 5 to 10 ml./min. In chronic hypoproteinemia 20 to 30 ml./kg. were infused daily by slow intravenous drip.

### Cadaver Blood for Transfusion.

Russian physicians have successfully transfused cadaver blood for about 30 years (Petrov, 1959). Blood drawn from cadavers within 6 to 8 hours after death retains its sterility and upon transfusion immediately begins to carry out its basic functions as an oxygen carrier. The clinical, esthetic, and scientific problems have been overcome, and the technic seems to be worth a thorough investigation (Kevorkian and Bylsma, 1961). The precautions of a thorough postmortem examination to preclude contagious diseases and certification by a pathologist to avoid incompatible blood types are necessary. It appears that this source of blood offers a tremendous potential in emergency cases where large amounts of blood are required immediately.

### Synthetic plasma-like colloids.

As described previously, there is no substitute for blood or blood plasma, but certain macromolecular colloids possess some of the physical properties of plasma. These are capable of maintaining the circulation volume by virtue of their osmotic pressure. The injection of the plasma substitute colloid attracts interstitial fluids into the blood vascular system. The large molecular size prevents the rapid escape of the injected material into the tissues or through the kidneys until the blood volume has been restored to normal. A plasma expander is an agent which will overcome the disparity of the circulatory system that exists in shock and thus tide a patient over a critical period until such materials as are specifically needed can be given, or until the patient can produce and disseminate enough plasma protein to restore his own blood volume.

**Dextran (Expandex, Gentran, Plavolex).** The dextran used clinically as a plasma substitute is a complex polysaccharide formed by the action of the bacterium *Leuconostoc mesenteroides* on sucrose. Chemically a number of dextrans are known to possess different structures, and they are prepared by different means. Sulfuric esters prepared from the dextrans are nontoxic anticoagulants that have been proposed as substitutes for heparin.

Bacterial dextran is a long chain polymer with a 1–6 glucopyranose linkage. The substance is not a pure material, and many small molecules are also formed in the bacterial and chemical purification processes. By means of partial hydrolysis and subsequent fractionation, the native dextran is reduced to a range of molecular sizes (average 75,000) to give a product with the desirable physical properties. As different manufacturers use different methods of preparation, the physical and chemical characteristics will differ. The dextran in 6 per cent concentration is a pale yellow, straw colored solution with a viscosity of 3.16 to 3.66 and an osmotic pressure of 65 to 70 cm. of water at 25°C. The usual dose is approximately 500 ml.

When a 6 per cent dextran solution is infused intravenously, the smaller molecules are excreted in the urine. From 25 to 40 per cent appears in the urine within the first 24 hours, with some excreted over the next 4 to 5 days. The larger molecules may be converted to glucose, and some may be found in the liver, spleen, and lymph nodes.

A 12 per cent solution of dextran in distilled water is also available for use in the adjunctive treatment of nephrosis. This salt-free solution increases the osmotic pressure of the blood plasma, relieving edema and enhancing diuresis. The diuresis that follows may be of short duration and does not seem to be greater than that produced by other intravenous diuretics. The 12 per cent solution of dextran may be considered as an adjunct in the general treatment of nephrosis.

In a patient receiving dextran labeled with radioactive carbon, over 90 per cent was eliminated in 10 days, 64 per cent in the urine, 26 per cent in the expired air as $CO_2$, and 2 per cent in the feces. Dextran has been used successfully in patients with cardiovascular and metabolic disease. A nitrogen- and phosphorus-sparing action was observed, indicative of retarded tissue protein catabolism. A prolonged bleeding time with no change in clotting time or platelet count was also observed. Some workers have found no evidence of renal function impairment, although liver and kidney damage has been reported in dogs after intravenous dextran injections.

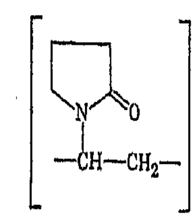
Dextran injection may cause varying degrees of allergic manifestations. These generally are not serious. They may be attributable to traces of nitrogenous substances from the bacterial production. The sensitivity reactions following dextran injections are more likely to be related to the antigenic action of the substance itself. The injection of as little as 1 mg. will produce skin erythema and wheal reactions. Massive doses are given intravenously; these may not cause serious allergic reactions because antibody production does not occur under these conditions. Current investigation is directed toward the elimination of impurities and the preparation of a more uniform product with a more narrow spectrum of molecular weights.

Dextran must be employed with great caution, if at all, in patients with pulmonary edema and congestive heart failure. Indeed the presence of myocardial disease and uremia makes the administration of dextran a hazardous therapeutic measure, although in certain cases it may be necessary. The increased bleeding time that follows the administration of dextran may not be apparent until several hours have elapsed. The prolongation of bleeding time presumably accounts for the hematuria, hematemesis, and surgical wound bleeding that has been observed after intravenous injections of dextran.

*Action of dextran on peripheral circulation.* Dextran solutions have been used by Moncrief *et al.* (1963) to prevent thrombosis of experimental vascular grafts in dogs and to treat thrombophlebitis in patients. The demonstration that dextran is capable of disrupting the agglutination of red blood cells occurring with "sludging" indicated that the substance might be effective in the therapy of venous thrombosis (Bryant *et al.*, 1962). The anticoagulant action of dextran sulfate, the bleeding tendency of patients following dextran injections, and the theoretical endothelial coating effect of dextran all suggested that physical changes in the cellular elements of blood would be produced. These changes were thought to be desirable in treating acute thrombophlebitis. A 6 per cent solution of dextran in saline was used in the patients. The dose was 1 per cent by volume of body weight in the first 24 hours. The second dose was ½ the initial amount the second day, and this dose was repeated daily as long as signs and symptoms persisted. Favorable results were obtained in all 11 patients in this initial study. Additional studies may determine the value of this form of therapy.

The effect of dextran on the peripheral circulation has made this substance useful in treating the shock syndrome of burns (Michie *et al.*, 1963), frostbite, and other clinical states associated with a restricted regional circulation. In these studies a low molecular weight dextran (average: 40,000) and a high molecular weight product (average: 185,000) have been used. It is too early to assess the true value and place of these products in the therapy of vascular diseases and trauma associated with peripheral vascular occlusion.

**Polyvinylpyrrolidone (PVP, Vinisil).** Polyvinylpyrrolidone is a synthetic high molecular weight polymer prepared by combining acetylene, ammonia, and formaldehyde. Through a series of reactions vinylpyrrolidone monomer is formed, which polymerizes to form PVP.



Polyvinylpyrrolidone
PVP

In the formula $x$ stands for the number of vinylpyrrolidone molecules which have united to form a molecule of PVP polymer. Some polymers are said to have an average molecular weight of 40,000 (range: 20,000 to 80,000). This is believed to be the most satisfactory form for use as a plasma substitute. As the conditions under which polymerization takes place are varied, products of different molecular weights are obtained.

PVP forms a water-soluble complex with iodine which is markedly reduced in toxicity when compared with the free halogen. The use of germicides containing PVP is discussed in Chapter 16. The toxicity and irritant properties of a number of chemicals are reduced by PVP. For example, the toxicity of potassium cyanide and nicotine for rats is decreased and the skin-irritating effects of detergents are reduced by the addition of PVP to the solution of these substances.

PVP solutions were stable, nontoxic, and nonantigenic in mice and rabbits. Mice tolerate the solution of PVP intravenously, but rabbits and dogs show immediate reactions unless a preliminary injection is given 24 hours in advance. PVP is nonantigenic for man, and allergic reactions have not been reported following the clinical use of this agent.

There have been several favorable reports on clinical experiences with PVP in this country. Most workers have used a 3.5 per cent solution in physiologic saline. As might be expected with a foreign substance of this character, much of the material is retained by the kidney glomerular membrane, and the substance is stored in the body for extended periods of time. The storage in the tissues, however, does not produce toxic effects.

PVP solutions have been used alone or with blood or plasma as effective adjuncts in supportive therapy in the management of shock. Their lack of antigenic, pyrogenic, and toxic reactions is noteworthy. It should be stressed that these preparations are for emergency use in instances in which whole blood or plasma is not available.

The ideal character of the molecular size has to be established for PVP, and additional clinical and animal experiments are needed to establish the optimal value. It is possible that future studies will elucidate this point.

**Gelatin solution, special intravenous (Plazmoid).** Gelatin, which is the incomplete protein derived from the collagen of bones and skin, can be made by several methods. A 5 or 6 per cent sterile, pyrogen-free, non-antigenic solution of gelatin in isotonic sodium chloride is used as an infusion colloid as a plasma substitute. This gelatin is prepared from refined beef bone collagen; it is apparently not antigenic. Many chemical degrading agents have been used to prepare a gelatin with the desirable physical and chemical properties. None of these products has been entirely successful.

The main disadvantages of gelatin solutions as plasma substitutes are the unknown fate of the unexcreted portion, the interference with blood typing, and the solid gels at room temperature of gelatin preparations. The first 2 objections may be overcome. Attempts to render osseous gelatins fluid by suitable chemical degradation processes have met with partial success.

Most commercial 5 and 6 per cent gelatin preparations become solid or semi-solid gels at ordinary room temperature or upon refrigeration. At 25°C they have a relative viscosity of from 5.45 to 14.0, depending upon the form supplied by the manufacturer. The solution is warmed to about 50°C before injection, and the solution must be kept warm for prolonged administration by slow intravenous drip. These properties are undesirable and militate against the use of gelatin solutions.

An oxypolygelatin has been studied that is prepared by condensing gelatin with glyoxal and subsequent oxidation with hydrogen peroxide. The resulting product has a molecular weight of 30,000 to 40,000, and it does not solidify at temperatures above 5°C. A 5 per cent solution of oxypolygelatin has a relative viscosity of 2.25 at 25°C. A modified fluid gelatin has been described which is prepared by chemically treating heat-degraded gelatin. This preparation is fluid at temperatures close to 0°C.

Gelatin solution in 5 or 6 per cent concentration is given intravenously in 500-ml. amounts. The effects on blood elements are not significant, and the osmotic action usually lasts for approximately 24 hours after a single infusion.

There seem to be few contraindications to the use of gelatin solutions intravenously except the presence of renal damage. Gelatin intravenously is excreted by the kidneys, and any serious medical or surgical condition that is associated with renal damage, *e.g.*, third degree burns, may prohibit the use of intravenous gelatin.

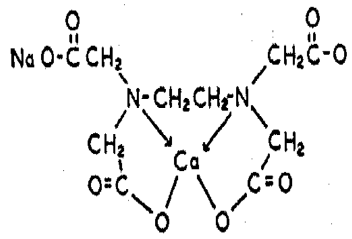
### DETOXIFYING AGENTS

In considering the toxicology of the various drugs in this text, reference has been made to agents used in treating the toxic symptoms by combining with the drug to detoxify it. These substances are chelating agents, organic thiols, or complexing agents that render the noxious substance less toxic. In general, the action of the detoxifying agents is one of solubility, and the most successful are those capable of complexing metal ions so that they no longer modify tissue enzyme functions.

Lipotropic agents have a protective action in preventing toxic hepatitis produced by phosphorus poisoning and other hepatotoxic substances. For this reason the lipotropic agents are considered in this section.

#### Calcium Disodium Edetate, U.S.P. (Versene, Endrate, Prochelate).

The successful treatment of lead and other types of heavy metal poisoning by means of this chelating agent centers around the unusual properties of the substance. Calcium disodium edetate is a cyclic complex chemical, as shown in the formula:



Calcium Disodium Edetate

Calcium disodium edetate may be considered as the monocalcium disodium salt of ethylene diamine tetraacetic acid (EDTA). In aqueous solutions or in the blood the molecule exchanges its calcium for the heavy metal ions to form a more stable, virtually nonionic, yet water-soluble complex. The heavy metal complex is excreted in the urine. This agent has been used in promoting the rapid excretion of stored lead from the body. The use of calcium disodium edetate in this manner involves certain hazards that must be understood.

**Pharmacologic effects of chelating agents.** Chelation is a unique chemical reaction in which a complex organic molecule combines with a metal ion to form a ring structure. The shared valances of the metal may or may not yield a complex that is ionized to any considerable degree. The ring structure may bind the metal so firmly that it is essentially unionized and thus unable to react chemically. The important feature of this unionized-metal complex is its solubility. Hence unlike ordinary chemical reactions, where the solubility product of the compound formed determines the rate and extent of the reaction, the chelation product remains in solution after formation. The ability of ethylene diamine tetraacetic acid (EDTA) to dissolve some insoluble metal salts and to prevent the formation of insoluble metal precipitates has suggested various clinical uses, *e.g.*, the dissolution of kidney stones. However, uncombined EDTA is toxic because of its ability to combine with the blood calcium. The monocalcium disodium salt of EDTA does not produce this effect and it can be injected intravenously or administered orally.

Calcium disodium edetate causes only a slight and short-lasting increase in the serum calcium, and only small amounts of the agent are retained in the body. This fact, and its low toxicity, suggested its use as a detoxifying agent in which the calcium in the molecule may be replaced by other metals in the treatment of heavy metal poisoning. It was proposed as a suitable antidote in nickel, copper, cadmium, cobalt, and lead poisoning by Plumb *et al.* (1950); and in radium, beryllium, and plutonium poisoning by Foreman (1953). At the present time calcium disodium edetate is considered to be potentially useful in treating poisoning by these metal ions, and in addition the agent has been used in porphyria and iron poisoning. In lead poisoning this substance has been used most successfully; indeed, it can be a diagnostic aid to determine whether a patient is suffering from chronic plumbism.

Many studies have shown that calcium disodium edetate does not exhibit any of the characteristic effects of calcium in influencing the coagulation of oxalated plasma, in compensating for hypocalcemic heart failure in the isolated heart-lung preparation, or in inhibiting the Bezold-Jarisch reflex in intact animals. This compound, therefore, is not to be used in specific calcium therapy but should be useful as a calcium-exchange substance to remove other metals from the body with which it can form soluble metal chelates.

**Dose of calcium disodium edetate.** Disodium calcium edetate is the treatment of choice in lead poisoning. It has been shown to be useful in plumbemia of *acute* lead poisoning and in the treatment of lead encephalopathy. It is claimed that this agent will only be effective in *chronic* lead poisoning if plumbemia is demonstrated. Some reports have suggested the oral administration of this chelating agent for the purpose of prophylaxis in industry where workers are exposed to potential chronic lead or other heavy metal intoxication. However it should be pointed out that its use in this manner is to be seriously questioned. Even assuming that the prolonged indiscriminate administration of the agent would be without hazard, it should not be considered as a substitute for poor industrial hygenic conditions which are corrigible.

Disodium calcium edetate is administered intravenously in either isotonic sodium chloride or 5 per cent dextrose solution. The concentration should not exceed 3 per cent. The suggested maximal dose is 0.33 gm. per 10 lbs. of body weight per day. The agent should be injected slowly at a rate not exceeding 0.17 gm. per 10 lbs. of body weight per hour. A course of treatment would consist of the injection of 2.5 gm. per 10 lbs. of body weight per week. A period of one week should elapse between treatments. Some workers have used a dosage period of only 2 or 3 days, alternating with a 4- or 5-day rest period. Oral doses of 250 mg. every 2 hours until a total daily dose of 2 gm. has been given have been tried on a weekly and monthly schedule by some workers. Bradley and Powell (1954) used a dose of 75 mg./kg./day in divided doses orally in 5 children for 9 days. Changes in the T-wave of the electrocardiogram occurred in 4 patients. These disappeared after discontinuance of the agent. Bessman *et al.* (1954) reported that approximately 1.8 mg. of lead was excreted for each 500 mg. of calcium disodium edetate administered. In their patients the dose was adjusted to achieve the maximal therapeutic efficiency. Increasing the dose of the chelating agent above an amount necessary to complex with the "available" lead does not increase the urinary excretion rate. Lead is bound to tissue protein sulfhydryl groups and is only slowly released. The chelating agent does not enhance the rate of release from the bound protein stores.

As a diagnostic test for lead poisoning the calcium disodium edetate is administered intramuscularly as a 20 per cent solution in doses of 75 mg./kg. The total dose is divided into 3 equal parts and injected at 8-hour intervals. A 24-hour urine sample will indicate the amount of lead excreted. An amount greater than 0.05 mg. Pb per L. indicates excessive ingestion of lead. In general, concentrations in excess of 0.05 mg. Pb/100 ml. of whole blood or 0.1 mg. Pb/L. of a 24-hour urine specimen is considered pathognomonic of lead poisoning.

The amount of urinary lead excreted after oral calcium disodium edetate therapy is much less than after intravenous administration. In acute lead poisoning and lead encephalopathy, intravenous dosage is superior.

Calcium disodium edetate may produce nephrosis. Daily urine analyses during treatment periods are necessary. Acute or chronic renal disease in the patient constitutes a severe limitation in the use of this chelating agent. The proper salt form of EDTA must be used. *Rapid injection of EDTA without the stoichiometric amount of calcium can be fatal.*

In acute lead poisoning in children cerebral symptoms may be enhanced at the beginning of treatment with the metal chelating agent. The seizures can be controlled by barbiturate administration. The dose is reduced if the patient has encephalopathy, and surgical intervention may be necessary to relieve the increased intracranial pressure.

Calcium disodium edetate has not significantly reduced the mortality from lead poisoning. It seems to be no more effective than BAL for terminating the acute episode of lead encephalopathy, but it appears to be more effective than BAL in reducing the incidence of residual neurologic damage.

Hardy *et al.* (1954) made a careful study of disodium calcium edetate in chronic lead poisoning in 3 individuals. They point out that the favorable results obtained are probably related to the increased excretion of lead but that a vacation from lead exposure would in time have produced the same result. However, the corresponding decrease in coproporphyrin excretion and reversal of the hematologic abnormalities with increasing lead excretion seemed to document the favorable effects of the agent. There was a tendency for decreased lead excretion with sustained administration of the agent. This may indicate different states of lead storage in the tissues as far as ease of mobilization of the chelate is concerned.

### Edathamil disodium (Endrate disodium).

Edathamil disodium is disodium ethylenediamine tetraacetic acid. This compound unites with divalent cations, such as calcium, to form chelates. Intravenous administration will decrease the serum calcium level. Endrate disodium is used in the treatment of hypercalcemia and digitalis intoxication to decrease the concentration of ionized serum calcium (see page 650). The recommended intravenous daily dosage is 50 mg./kg. diluted with 500 ml. of glucose solution or saline. The infusion time is 2.5 to 4 hours. The presence of renal disease is considered a contraindication.

Disodium or trisodium ethylenediamine tetraacetic acid is not employed in the treatment of heavy metal poisoning. These salts or the free acid EDTA should not be confused with the calcium disodium edetate intended for use in the treatment of multivalent cation metal poisoning. Caution is recommended in the infusion of edathamil disodium in patients who may have potassium deficiency states. Batchelor *et al.* (1964) found that the agent produced a 2- to 6-fold increase in urinary potassium excretion following the injection of 3 gm. in 500 ml. of distilled water. The potassium loss may be sufficiently serious to produce potassium-depletion nephropathy and neprotoxicity.

### Dimercaprol, U.S.P. (BAL).

Dimercaprol was developed as an antidote for use against the arsenical chemical warfare agents. It is 2,3-dimercaptopropanol, commonly called BAL. BAL is effective in acute poisoning caused by compounds of arsenic, gold, and mercury. In experimental animals the agent is effective in treating poisoning caused by salts of antimony, bismuth, chromium, nickel, and mercury. It is not useful in iron, thallium, lead, or selenium poisoning; in fact, an increased toxicity is observed with lead or selenium. In man, the virtues of BAL therapy in antimony and bismuth poisoning are doubtful.

Dimercaprol is an organic dithiol that combines with metal ions. The —SH groups of the molecule form more stable complexes with the metal than do the corresponding cellular enzyme proteins. The resulting combined form of BAL-metal must be excreted by the body. Dimercaprol is a liquid with an offensive, mercaptan-like odor.

**Dose of dimercaprol.** In acute mercury and arsenic poisoning the prompt administration of the initial dose of 3 ml. of a 10 per cent oil solution of BAL (Dimercaprol Injection, U.S.P.) intramuscularly is important for successful therapy. The usual antidotal treatment must not be omitted. The injection is repeated every 4 hours until 4 to 5 such doses have been administered. In no case should a total dosage of 35 mg./kg. during 36 hours be exceeded. The blood and urinary mercury level may serve as a guide to further treatment.

Reactions to BAL such as nausea, generalized aches, and a burning sensation of the eyes and mouth may be experienced by the subject. The blood pressure is frequently raised, and occasionally there may be a sense of constriction of the throat and chest. These symptoms do not last longer than 30 to 60 minutes. The compound has no cumulative toxicity from the usual course of treatment.

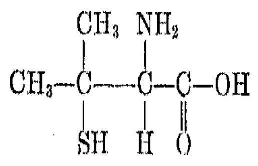
### Penicillamine (Cuprimine).

A new group of antidotes for heavy metal poisoning was discovered in derivatives of the sulfhydryl amino acid, penicillamine ($\beta,\beta$-dimethylcysteine or 3-mercaptovaline).

Walshe (1956) first demonstrated that penicillamine was useful in treating a disease characterized by hepatolenticular degeneration called Wilson's disease. Penicillamine combines with metal ions, and it has been used as an antidote for heavy metal intoxication (Done, 1961).

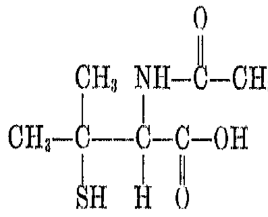
A number of isomeric forms of penicillamine are available. Cuprimine is the *d*-isomer. This

substance is a white, crystalline powder. Although it has a *d* configuration it is levorotatory ($[\alpha]_d^{25°} = -63° \pm 5°$; C = 1, in 1N. NaOH). The substance is soluble in water and the solutions are comparatively stable at pH 2 to 4. The compound forms hydrochloride and sodium salts.



$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle SH}{|}}{C}}-\overset{\overset{\displaystyle NH_2}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}-OH$$

Penicillamine



$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle SH}{|}}{C}}-\overset{\overset{\displaystyle NH-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}-OH$$

N-acetyl Penicillamine

**Penicillamine in metal poisoning.** Aposhian and Aposhian (1959) demonstrated that the lethal effects of mercuric chloride in rats could be counteracted by *d*-penicillamine, *dl*-penicillamine and N-acetyl-*dl*-penicillamine. The acetyl derivative was the most effective and least toxic. The greater toxicity of the *dl*-form over *d*-penicillamine or N-acetyl-*dl*-penicillamine seems to be associated with the *l*-penicillamine isomer. *l*-Penicillamine has an anti-vitamin $B_6$ activity *in vivo* and causes a rapid loss of $B_6$ from the body.

The mechanism underlying the protective action of penicillamine is unknown. The structure of the metal-penicillamine complex has not been determined. It is presumed that the thiol group is important, but the mechanism is probably more complicated than direct reaction between sulfhydryl groups and metal, for other mono-thiols such as cysteine and glutathione are not equally protective. According to Aposhian, *l*-amino acid oxidase and *d*-amino acid oxidase catalyze a rapid breakdown of cysteine but not *l*-penicillamine or acetyl penicillamine. *d*-Penicillamine is oxidatively deaminated quite slowly. This stability to enzyme degradation may account for the activity of penicillamine as a heavy metal antidote.

Boulding and Baker (1957), in treating 2 cases of lead poisoning, administered orally 0.3 gm. of penicillamine 3 times a day 30 minutes before food was eaten to avoid complexing with metal ions in the diet. Harris (1958) used the same dosage regimen in 2 patients with lead poisoning. The results were compared with periods of therapy on intravenous calcium disodium edetate. Elimination of lead was slightly greater with calcium disodium edetate, but the ease of oral administration of penicillamine, its lower cost, and lower toxicity made this agent slightly superior.

**Penicillamine in Wilson's disease.** Penicillamine has an established place in Wilson's disease. This disease, more correctly designated as hepatolenticular degeneration, is caused by an inherited familial defect that results in an abnormality in copper metabolism. The subject has a positive dietary copper balance, in contrast to the normal zero copper balance. Although the consequent chronic copper toxicity may not be manifest until adult life, the diagnosis can be made in the asymptomatic young patient.

The symptoms of Wilson's disease are jaundice, ascites, and edema. Characteristic corneal copper deposits can be recognized in the outer margin with smoky, brownish rings (Kayser-Fleischer rings). Skin discoloration may be observed. The most prominent symptoms are related to the central nervous system; shrinkage and cavitation of the basal ganglia are pathologic findings. The subject has difficulty in concentrating his thoughts, assumes a fixed, smiling expression, and exhibits choreic movements with pill-rolling gestures of the fingers and plastic rigidity of the limbs; dystonia and dysarthria are evident.

The diagnosis of Wilson's disease is based upon the history of the patient and a low serum concentration of ceruloplasmin. In addition, a high concentration of copper must be found in a biopsy specimen of the liver in a patient without symptoms. Hepatic copper concentrations range from 260 to 1500 $\mu$g./gm. of dry liver. Normal values are less than 50 (Sternlieb, 1963).

Penicillamine increases urinary excretion of copper in patients with Wilson's disease. When the agent is used with a copper-restricted diet and the oral use of potassium sulfide or a cation exchange resin to precipitate a large portion of any ingested copper, it is possible to produce a marked neurologic improvement in the patient. The treatment must be continued for many months before a significant improvement can be noticed in some patients. BAL has also been used in patients with Wilson's disease, but penicillamine is effective orally (Strong *et al.*, 1961).

Initial dosage is 1 gm. of penicillamine in divided doses by mouth for adults and older children. Subsequent dosage is based on urinary copper excretion. Dosage may be increased to 4 to 5 gm. per day, but larger doses do not usually increase the cupriuria. The goal is to keep the patient in a negative copper balance.

Patients taking penicillamine should be kept under close observation for the appearance of toxic reactions of extravasation of blood into the skin, pyridoxine or iron deficiency, and changes in blood and platelet count and in the hemoglobin level.

The discovery of the value of penicillamine in this relatively rare inherited metabolic defect is of considerable significance. Not only does this provide a means of therapy of a life-threatening disease, but the treatment of diagnosed asymptomatic patients may eventually permit the use of the agent prophylactically to avoid the onset of the pathologic effects.

## LIPOTROPIC AGENTS AS DETOXIFYING AGENTS

The lipotropic agents are substances that influence fat metabolism; they hasten the removal of, or decrease the deposition of liver fat. Choline, inositol, methionine, and betaine possess this property. Choline has been most widely used as a lipotropic agent. The effects of these agents in treating the symptoms of fatty infiltration of the liver are most marked. The lipotropic agents have also been employed with limited success in atherosclerosis, arteriosclerosis, and various disorders of lipid metabolism.

### Choline.

Choline is a dietary essential that has been classified as a member of the vitamin B complex group. It may be the parent substance from which acetylcholine is formed by enzymic action.

Choline is a nitrogenous base and forms crystalline salts. Choline bitartrate and the dihydrogen citrate salts are used for oral therapy and are stable in tablet form. The perchlorate salt is a stable, non-hygroscopic form suitable for laboratory use. Choline is trimethyloxyethyl-ammonium hydroxide (see page 530).

Choline is a component of the phospholipid *lecithin*, an important cell constituent. Choline deficiency states in animals are manifested by a deposition of neutral fat in the liver, hemorrhagic degeneration of the liver and kidneys, involution of the thymus, and splenic enlargement (Best *et al.*, 1952).

The development of fatty livers by depancreatized dogs led C. H. Best and his associates to a realization of the "lipotropic" action of choline. This action is described as the prevention of fatty livers in animals by the administration of choline. The mechanism appears to be through an interchange of fats and phospholipids in the liver that requires choline for its normal course.

Choline through the phospholipids is believed to play an important role in the maintenance of normal fat transport in the body, although only very fragmentary data have been made available. For example, very little is known concerning the relationship between choline and the levels of blood lipid fractions in health or disease. Substances are known that stimulate phosphatide turnover, but these are not lipotropic agents. Snyder *et al.* (1957) compared the lipotropic and phospholipid turnover actions of choline, betaine, and inositol in rats on low and high fat diets. All 3 agents caused a significant reduction of total lipides in the liver on low-fat diets. Only choline and betaine caused a reduction of total liver fat in rats on a high-fat diet. All 3 compounds increased phospholipid synthesis, but only choline and betaine stimulated lipid phosphorylation in rats on high-fat diets. One would expect the amine salts to possess a different mechanism of action from that of the polyol, inositol.

Experimental evidence points to the importance of choline as a source of methyl groups for certain metabolic reactions. In furnishing a "labile" methyl group, choline is able to support the growth of rats on a homocystine diet in the absence of the essential amino acid methionine. The process of transmethylation is an important factor in human metabolism, and the body's need for labile methyl groups, as in choline, is becoming increasingly evident. Methionine also is used for the clinical prophylaxis and treatment of hepatic injury.

**Lipotropic use of choline.** Choline therapy in liver cirrhosis has yielded satisfactory results when combined with other therapeutic measures such as high protein, vitamin, and special carbohydrate diets. Choline has been administered in combination with cystine by a number of investigators. In those cases benefited by this treatment a decrease in liver size is noted, ascites and edema may be decreased or eliminated, and liver function tests show an improved physiologic function.

Choline is only partially effective in treating

fatty liver caused by phosphorus poisoning or other kinds of liver toxicity that are not directly concerned with choline metabolism. Choline has been used in the treatment of icterus gravis in babies and in certain of the anemias.

Because choline is apparently involved in the regulation of blood lipid levels, attempts have been made to use this substance to control atherosclerosis. The evidence for its clinical usefulness for this purpose is equivocal.

**Choline Dihydrogen Citrate, N.F.** Two or more 0.6-gm. tablets of choline dihydrogen citrate may be given several times daily. Individual tolerance may determine the total dosage. Toxic effects consist of nausea and a slight fall in blood pressure. Daily dosage has been found to be variable and must be adjusted to the individual's tolerance.

**Choline Bitartrate, N.F., Choline Succinate,** and **Choline Gluconate** are salts of choline that have the same action and uses as the other salts of choline. Choline gluconate is available as a flavored solution containing 0.62 gm. of choline gluconate in each ml.

### Methionine, N.F.

This essential amino acid is active in preventing fatty livers owing to choline deficiency. Thus, like choline, it is said to elicit a lipotropic effect. The liver damage caused by chloroform inhalation in protein-depleted dogs is prevented by methionine. It will partially protect experimental animals from liver damage by other hepatotoxic drugs. For this reason the substance has been used clinically on an experimental basis in the treatment of hepatic cirrhosis, acute hepatitis, and liver dysfunction resulting from carbon tetrachloride and trinitrotoluene (TNT) poisoning. Methionine is used in these cases to supplement standard methods of therapy.

As a supplement to a high-protein diet, from 3 to 6 gm. of methionine is administered daily in tablet form. It may be combined with choline administration. Large doses up to 20 gm. have been used. Gastrointestinal distress is the chief untoward symptom that has been reported following its use. In patients with severe liver disease the toxemia may be exaggerated by large doses of methionine. *Methionine Capsules, N.F.* and *Methionine Tablets, N.F.*, usually available, contain 0.5 gm. of methionine.

### Inositol, N.F. ($C_6H_6(OH)_6$).

Inositol is hexahydroxycyclohexane, a white, crystalline powder, soluble in water. Seven optically inactive forms and a pair of active isomers of inositol can exist. Only the optically inactive *i*-inositol is physiologically effective. Inositol is odorless and has a sweet taste that is characteristic of the sugar alcohols. The nitrate ester is employed as a depressor vasodilator drug.

Experiments have indicated that inositol may play a role in preventing fatty livers in animals on experimental diets. Both choline and inositol have been reported to be partially effective as lipotropic agents for biotin deficiency-produced fatty livers in rats. Some reports have shown that inositol prevents the fatty livers of rats fed a fat-free, high-carbohydrate diet supplemented with biotin and folic acid. Other workers have been unable to demonstrate a lipotropic effect from inositol feeding.

Most of the experimental evidence has indicated that inositol plays a role in the nutrition of the animal body closely associated with the vitamins and other nutrient essentials. Inositol has not been shown to be essential in the human diet. Inositol is of no value in the treatment of arteriosclerosis obliterans, and as a lipotropic agent it does not modify significantly the atherosclerotic process.

It is evident that more experimental evidence will be required to determine the metabolic role of inositol in human nutrition. At present inositol is used in the treatment of hepatic cirrhosis, toxic hepatitis, and functional liver impairment. It is generally prescribed with choline and methionine. *Inositol Tablets, N.F.*, usually available, contain 0.25 and 0.5 gm. of inositol.

## AGENTS USED TO REDUCE HYPERCHOLESTEROLEMIA

Atherosclerosis is the most important cause of degenerative vascular disease. Coronary artery insufficiency, cerebral hemorrhage, and thrombosis are clinical manifestations of atherosclerosis. Numerous references have been made in the text to the drugs used in treating these diseases. In attempts to inhibit and control the atherosclerotic process, dietary adjuncts such as the lipotrophic agents and nicotinic acid have been fed experimentally to animals and employed in therapy in man. Other dietary measures, notably low-fat diets, have been tried, and recently the sitosterols have been used. In order to understand these therapeutic measures, a brief outline of the theoretical aspects of atherosclerosis is presented (Steinberg, 1962).

It appears that atherosclerosis is essentially a metabolic disorder characterized by faulty transport, distribution, and deposition of lipids. It is influenced by diet and such factors as heredity, sex, stress, and associated metabolic diseases, especially diabetes mellitus. Some hold the view that atherosclerosis is initiated by the laying down of fibrin by vascular endothelial cells and the secondary deposition of lipid in this cellular cushion. The concept of a metabolic disorder associated with hypercholesterolemia and a subsequent atherosclerosis has become an attractive hypothesis.

The rationale for the use of agents to reduce hypercholesterolemia is based upon the finding, not entirely accepted, that elevated blood cholesterol levels and atherosclerosis and its clinical complications are related. Cause and effect relations between these two variables has not been proved. The studies of Zilversmit *et al.* (1961) and Newman *et al.* (1961) provided evidence that the phospholipids of the aorta in man and animals arise primarily from synthesis *in situ*. Studies of the free and esterified cholesterol in the normal and diseased aorta indicate that these lipid fractions are derived from blood serum (Swell *et al.*, 1963). There is no general agreement on the changes in cholesterol ester composition in the human aorta associated with atherosclerosis.

The theory that cholesterol and fats are related to atherosclerosis is supported by postmortem studies. The atherosclerotic plaques from the intima of the aorta are rich in cholesterol esters. These apparently are derived from the blood serum cholesterol. Rabbits fed high-cholesterol diets develop atheromas similar to those observed in man; however, there are fundamental differences in the nature of the lesions.

Other types of experimental atherosclerosis have been studied. Estradiol in young cockerels and ACTH in rats produce a variety of atherosclerosis suitable for experimental studies. Various types of hypercholesterolemic diets have been fed with experimental endocrine modifications in rats and rabbits. These laboratory methods permit experimental trials that may shed light on the nature of the atheromatous process.

Deposition of cholesterol plaques may be related to the solubility of the blood lipoproteins containing cholesterol. Solubility could be influenced by changes in the levels of the blood fatty acids, heparin, and phosphatides. Blood alpha and beta lipoprotein fractions have been separated by electrophoresis. The beta fraction contains 75 per cent of the blood cholesterol. This fraction is usually elevated in atherosclerosis, while the alpha lipoprotein fraction is depressed.

In addition, high-fat diets in various groups of people have been related to the incidence of atherosclerosis. Some native populations have a low-fat diet and also a low incidence of atherosclerosis. However, most native low-fat diets are also low in protein and may be deficient in vitamins, and it is impossible to incriminate fat alone.

Psychosocial relationships, in addition to dietary cholesterol, have been suggested as important in determining the incidence of cardiovascular disease and atherosclerosis. In a study of this problem several investigators have measured the dietary cholesterol and blood cholesterol levels of monks. These men are subjected to similar psychosocial forces; however, their dietary habits are fundamentally different. In 2 religious orders markedly different serum cholesterol levels were observed. There was a similar low incidence of coronary artery disease in both groups. This observation does not equate with the concept of high blood cholesterol levels and increased susceptibility to coronary attacks (Nutrition Abstr. & Rev., 1963).

The nature of the dietary fat seems to be significant. Animal fats and hydrogenated (saturated) vegetable oils raise the serum cholesterol, while unsaturated fish oils and natural vegetable oils tend to lower the serum cholesterol. Although cholesterol has been shown to be closely associated with atherosclerosis, it is generally agreed that it is not the sole factor in the etiology of the disease.

The American Heart Association's Central Committee for Medical and Community Program (1961) reported on dietary fat and its relation to heart attacks and strokes as follows:

> "The reduction or control of fat consumption under medical supervision, with reasonable substitution of poly-unsaturated for saturated fats, is recommended as a possible means of preventing atherosclerosis and decreasing the risk of heart attacks and strokes. This recommendation is based on the best scientific information available at the present time.
>
> "More complete information must be obtained before final conclusions can be reached. Such information can be obtained only through intensified research into the causes and prevention of atherosclerosis—a program to which the American Heart Association is fully dedicated."

Because it is impracticable for a person to add enough unsaturated fats to an otherwise unchanged diet to bring about any significant reduction in the blood cholesterol, other approaches to the problem are desirable. Chemical agents that reduce the total cholesterol absorption and enhance fecal excretion of cholesterol provide an experimental type of therapy in atherosclerosis.

A résumé of the chemistry and physiology of the lipids in the diet with indications for restricting the total fat content of the diet has recently been prepared (A. M. A. Council on Foods and Nutrition Report, 1962).

### Sitosterols, N.F. (Cytellin).

Sitosterols are a mixture of 80 to 90 per cent $\beta$-sitosterol and 10 to 20 per cent dihydro-$\beta$-sitosterol. $\beta$-sitosterol is a plant sterol which is chemically identical with cholesterol, except for an ethyl group on the side chain. Dihydro-$\beta$-sitosterol has a saturated ring. The sitosterols apparently enhance the fecal excretion of cholesterol. They accomplish this presumably by interfering with the absorption of cholesterol from the intestine. Thus less exogenous cholesterol from food is absorbed and endogeneous cholesterol secreted in the bile is not reabsorbed. The serum cholesterol level is lowered as a result of the sustained decreased absorption of this substance. The commercial product is a 20 per cent suspension of the sitosterols. Oral dosage is individualized to produce the desired degree of lowering of the blood cholesterol. Doses of about 10 gm. per day orally are usually given, divided before and after meals.

Sitosterols have been used in the reduction of the hypercholesterolemia of diabetes mellitus, hypothyroid states, nephrosis, and xanthomatosis. There is little agreement as to its value in atherosclerotic disease. The sitosterols have not produced serious toxic effects in patients to whom they have been administered in large doses. Their ultimate toxicity is unknown. According to Shipley *et al.* (1958) the feeding of $\beta$-sitosterols to human beings for periods exceeding 4 years has not produced adverse effects.

Berkowitz *et al.* (1959) employed a test utilizing radioactive triolein to reveal the fate of ingested fat and how sitosterol might influence fat absorption. They used 5 normal control subjects and 5 patients with severe coronary artery disease. Their results indicated that sitosterol does not decrease neutral fat absorption when given immediately before a fat meal. Prolonged treatment (6 months) with the sitosterols in patients with coronary artery disease and hypercholesterolemia did not significantly alter the blood cholesterol level except in 1 patient. They suggest that the spontaneously-occurring fluctuations in serum cholesterol values make the interpretations of experimental trials difficult. No case showed any improvement in fat tolerance even though the serum cholesterol level fell. These workers feel that reliance on blood cholesterol levels alone is probably an incomplete guide to the effectiveness of the agent in combating atherogenic effects.

### Safflower oil (Saff, Safflor).

Safflower oil is the fixed oil extracted from the seeds of the safflower *Carthamus tinctorius*. The oil contains 74.5 per cent linoleic acid, an essential unsaturated fatty acid, and 6.6 per cent of mixed saturated fatty acids. Safflower oil is a 65 per cent emulsion of the oil intended for oral use.

When given in sufficient quantities and replacing animal fats and hydrogenated vegetable oils, the unsaturated fatty acids of corn, cottonseed, and safflower oil will lower serum cholesterol levels. To have any effect these substances must replace the saturated fatty acids already in the diet. The suggested daily dose of safflower oil is 75 ml. of the emulsion given in divided doses. This dose provides about 450 calories, and weight gain may be expected if the regular dietary caloric intake is not adjusted accordingly.

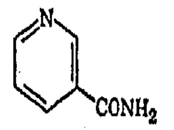
### Heparin potassium (Clarin).

This salt of heparin is used only for the management of atherosclerosis. Heparin causes a change in the lipid and lipoproteins of blood, and this action is discussed under heparin sodium in Chapter 44. The potassium salt is not intended to be used as an anticoagulant.

Heparin potassium is administered sublingually in the form of tablets. The usual dose is 1500 International Units 3 times daily after meals. These doses have no effect on the blood clotting time of the patient, and adverse effects have not been reported. Its use in treating atherosclerosis is experimental at the present time.

### Nicotinic Acid, U.S.P.

Nicotinic acid (niacin, pyridine-3-carboxylic acid) is equivalent to the amide from the standpoint of therapeutic effectiveness.



Nicotinamide, U.S.P.

Pharmacologically there are differences between the 2 compounds. The administration of either of these compounds in proper doses leads to a disappearance of all alimentary, dermal, and other lesions characteristic of the dietary deficiency disease, pellagra. Some of the various manifestations of pellagra are apparently not due to a deficiency of a single vitamin but probably represent a lack of several vitamins of the B complex group.

**Nicotinamide Injection, U.S.P.** is a sterile solution of nicotinamide in water. In ampule form the solution is usually available in 100-mg. doses, 2 ml. for parenteral use. *Nicotinamide Tablets, U.S.P.* for oral administration usually contain 25 and 50 mg. of nicotinamide per tablet. Capsules are also available. *Nicotinic Acid Tablets, U.S.P.* for oral use are available containing 25, 50, and 100 mg. of nicotinic acid per tablet. Capsules are also available. The adequate daily dietary requirement in the treatment of human pellagra for nicotinic acid or nicotinamide appears to be from 15 to 20 mg.

**Pharmacologic effects of nicotinic acid.** Nicotinic acid evokes marked vasodilatation. Administration of oral or parenteral doses of 30 mg. produces a marked flushing of the face and neck and a transient, mild fall in blood pressure, Nicotinamide does not produce these effects and is the compound employed for parenteral use in the treatment of pellagra. Nicotinylalcohol tartrate is the vasodilator drug Roniacol.

Nicotinic acid functions as an integral part of 2 different coenzymes which act as prosthetic groups for several metabolic enzymes. These prosthetic groups are coenzyme I (cozymase, DPN) and coenzyme II (triphosphopyridine nucleotide, TPN). These are water-soluble coenzymes. The prosthetic groups of these enzymes are unusual in that they are only loosely associated with the protein part of the enzyme system. They have been called the mobile coenzymes. The important role they play in metabolic reactions is rapidly being elucidated.

Nicotinic acid causes gastric irritation in high doses. A case of bilateral amblyopia has been reported in a patient taking 6 gm. of nicotinic acid daily for 1 year. This effect disappeared when the drug was discontinued. Cholestatic jaundice may be produced occasionally by the drug, but the liver function returns to normal when the drug is stopped. A rise in serum uric acid may follow the administration of large doses of nicotinic acid. In general, the drug is not a toxic substance.

**Nicotinic acid in atherosclerosis.** When a daily dose of from 1.5 to 6 gm. of nicotinic acid is administered to patients with hypercholesterolemia and an abnormally high ratio of beta-lipoprotein cholesterol to alpha-lipoprotein cholesterol, the plasma cholesterol has decreased significantly in the majority of the patients over a 12-week period. The beta:alpha cholesterol ratio was reduced. The total lipid level in the plasma is reduced in most patients, but to a lesser degree than was the cholesterol concentration. Doses greater than 3 gm. daily are required in most patients to maintain the blood cholesterol levels at normal limits. When nicotinamide is substituted for nicotinic acid, blood cholesterol levels rise to values as high as those observed before treatment.

Altschul and Hoffer (1958) reported that large doses of nicotinic acid decreased serum cholesterol levels. Hypercholesterolemic levels in patients were decreased more than were normal levels in healthy young men. Similar observations had been made in rabbits. Nicotinamide had no influence on serum cholesterol levels. These observations have encouraged the study of nicotinic acid in atherosclerosis in patients with hypercholesterolemia.

It has been reported that nicotinic acid will induce fibrinolysis *in vivo* when 1 to 3 mg./kg. is injected intravenously in human subjects. Clot firmness was measured in blood specimens collected after the injection of the drug. The effect was maximal after 10 to 15 minutes. Nicotinic acid did not exert this action *in vitro*.

Achor *et al.* (1961) followed their earlier observations with nicotinic acid in hypercholesterolemia and found that the decreased plasma cholesterol could be maintained for periods exceeding 1 year. The effect disappears when the treatment is stopped. They used oral doses of 1.5 to 6 gm. per day for 3 months to 1½ years. The degree of response to treatment varied widely but was reasonably reproducible for each person. Those patients with high initial concentrations of plasma cholesterol usually responded better to nicotinic acid treatment than did those with lower cholesterol values. These workers noted that there were no cases of increase in severity of angina pectoris and that some subjects experienced less anginal pain.

The large doses of nicotinic acid used in this form of therapy caused flushing, pruritus, and some nausea and vomiting. The cutaneous flushing and pruritus were most marked at the beginning of treatment but subsided rapidly.

The mechanisms by which nicotinic acid lowers plasma cholesterol levels remain obscure. Schade and Saltman (1959) reviewed the various proposals that have been advanced. In their own work they observed that there is a marked inhibition of the rate of cholesterol synthesis by liver slices from animals fed nicotinic acid. Since the principal detoxication product of large doses of nicotinic acid is *nicotinuric acid*, it was proposed that the inhibition of cholesterol synthesis occurs as a result of competition of lipid-synthesizing and detoxication systems for the limited amount of coenzyme A in the liver cell. This view is shared by other workers, who contend that the metabolite nicotinuric acid is responsible for the lowering of blood cholesterol.

Altschul (1958) implies that nicotinic acid is converted to either DPN or TPN, which in turn enhances the oxidative metabolism of cholesterol. This seems unlikely, since nicotinamide, the active moiety of these coenzymes, is ineffective. Other workers have proposed that nicotinic acid alters the chemical distribution of cholesterol in the blood by activating the reticuloendothelial system. O'Reilly *et al.* (1957) proposed that heparin release from mast cells may account for the antilipemic action. The administration of heparin is known to lower hyperlipemia, and the 2 effects, heparin release and depression of blood cholesterol levels, may be associated with nicotinic acid administration.

Perhaps most important is the fact that the exact relationship between blood cholesterol levels and the incidence of coronary artery disease remains unproved. The cause and effect relationship between elevated cholesterol levels and cardiovascular disease is polemic. Like the use of sitosterols in atherosclerosis, the use of nicotinic acid in hypercholesterolemia may be justified on the basis of its apparent safety and the relative inadequacy of other forms of therapy.

## SCLEROSING AGENTS

The intravenous injection of an irritating chemical will injure the intima of blood vessels and produce an intravascular clot. If the irritating substance is injected into a branch of a small superficial vein, the clot formed will be sufficiently large to occlude the lumen of the vessel. Further, if by application of a pressure bandage the vein is prevented from enlarging, fibrous tissue develops and permanently closes the circulation in the vessel. Sclerosing agents are irritating substances employed in this manner primarily in the occluding of varicose veins.

Many irritating chemicals have been used as sclerosing agents. At the present time only 3 seem to be widely used: they are sodium morrhuate, sodium tetradecyl sulfate, and sodium psylliate.

**Sodium Morrhuate Injection, U.S.P.,** is a sterile solution of the sodium salts of the fatty acids of cod liver oil. It is usually injected as a 5 per cent aqueous solution with from 0.5 to 3 per cent ethyl or benzyl alcohol. A test dose of 0.5 ml. of the solution is administered intravenously to determine whether the patient is hypersensitive to the drug. If no contraindication exists, 2 to 3 ml. of the solution may be injected 2 to 3 times weekly, following the special technics for the treatment of the varicosity.

**Sodium tetradecyl sulfate (Sodium Sotradecol)** is sodium 7-ethyl-2-methyl-4-hendecanol sulfate. The substance is a white, waxy, odorless solid, soluble in water. Depending upon the size of the veins and hence the dilution with blood, a 1, 3, or 5 per cent solution is employed. The commercial solution contains 2 per cent benzyl alcohol.

Sodium tetradecyl sulfate is a surface-active wetting agent that possesses sclerosing properties. It has been used for the obliteration of varicose veins and internal hemorrhoids that are not prolapsed or thrombosed. It causes pain at the site of injection and sloughing if some of the solution is allowed to leak outside the lumen of the vein. Toxic reactions have not been reported, and sensitization reactions are rare and generally of a mild character. The amount injected at any one site is not more than 1 ml., and a total dose for a single treatment period should not be more than 6 ml. of a 5 per cent solution.

**Sodium Psylliate Injection, N.F. (Sylnasol)** is a sterile solution of the sodium salts of the fatty acids obtained by the hydrolysis of the fixed oil of the seeds of *Plantago ovata* (see page 262). A 5 per cent solution containing 2 per cent benzyl alcohol is injected intravenously as a sclerosing agent. When injected, sodium psylliate irritates the endothelium of the vein and causes a local thrombosis. Serious allergic reactions may develop after the injection of this sclerosing agent. For this reason a preliminary test dose of 0.5 ml. should be injected and a total single dose should not exceed 6 ml.

### Dental Prophylactic

**Sodium Fluoride, U.S.P.** A 1 to 2 per cent solution of sodium fluoride is applied topically to the teeth of children in dental practice to achieve protection against caries. The chemical produces a hardening effect upon tooth enamel. Fluorides are also added to some municipal water supplies in concentrations of 0.7 to 1.3 parts per million of fluoride ion to decrease the incidence of dental caries.

**Stannous fluoride** has been used in dental practice in the prevention of caries in place of sodium fluoride. A single application of an 8 per cent solution of stannous fluoride at 6-month or yearly intervals will reduce the incidence of dental caries in school children more effectively than the application of a 2 per cent sodium fluoride solution 4 times during a 10-day period. The solution must be freshly prepared because solutions of stannous fluoride tend to oxidize to the stannic form, and hydrolysis of the compound to form insoluble stannous hydroxide will take place. This tin compound also has been incorporated successfully into a dentifrice.

**Toxicity of fluorides.** When ingested, inorganic fluoride salts are toxic, and because they are widely used in insecticidal powders, the nature of fluoride poisoning and its treatment is considered.

Ingestion of large amounts of fluorides will cause nausea, epigastric pain, and excessive salivation. After absorption of fluorides the blood calcium level is lowered because insoluble calcium fluoride is formed. Fluorides are enzymic poisons; they inhibit anaerobic glycolysis, lipase, phosphatase, and cholinesterase. It is assumed that their toxic effects are more likely to be related to enzyme inhibition than to calcium depletion.

When toxic amounts of fluorides have been ingested, gastric lavage with 1 to 5 per cent calcium chloride solution or lime water should be instituted as soon as possible. Systemic effects may be treated by intravenous 10 per cent calcium gluconate solution.

Chronic toxicity from exposure to fluorides may be encountered in industrial uses of these chemicals and in persons living in regions where the drinking water contains excessively high concentrations of fluorides (above 1.8 parts per million). The first signs of chronic intoxication are mottled tooth enamel and joint stiffness. Eventually, bone tissue becomes more opaque to x-rays, and there is ligament calcification and deformation of bone structure.

Fluorine in organic combination is usually very stable chemically, and the fluoride ion is not formed *in vivo* when these substances are used as drugs. Interesting pharmacologic changes are brought about by the introduction of fluorine atoms in a drug molecule replacing hydrogen atoms. For example, trifluoroethyl vinyl ether is a very potent general anesthetic; triflupromazine and trifluoperazine are potent phenothiazine derivatives. On the other hand, the aliphatic fluorocarbons known as the Freons are pharmacologically inert.

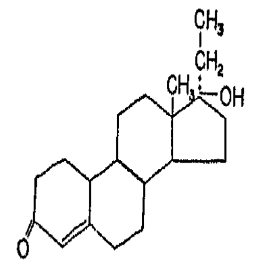
### Protein Anabolism

Androgens are known to exert an influence on protein metabolism as well as to influence the gonads and to cause the development of secondary sex characteristics. Androgens cause an anabolic effect in the adolescent male and protein metabolism is promoted. This encouragement of protein anabolism is demonstrated by rapid growth and muscular development. Thus testosterone is both androgenic and a protein anabolic agent. The pharmacology of these agents is considered in Chapter 49.

In an attempt to separate these 2 actions, numerous alterations in the structure of the steroids have been made and studied. Nortestosterone was found to provide a wide separation of the androgenic effects from the protein anabolic properties. This led to the discovery in 1953 of 1

compound that exhibited low androgenic action and a high protein anabolic potency. This substance is $17\alpha$-ethyl-17-hydroxy-19-nor-4-androsten-3-one, known as norethandrolone. A number of synthetic anabolic steroids have been prepared in recent years.

**Norethandrolone (Nilevar).** Norethandrolone belongs to the steroid class of drugs. It is also known as *19-Nortestosterone.* Its structure is shown in the following formula:



Norethandrolone
Nilevar

Norethandrolone is a white, crystalline substance, relatively insoluble in water but soluble in organic solvents.

The increase in weight of the *levator ani* muscle in castrated male rats produced by a steroid is termed the *myotrophic effect.* The androgenicity is studied by determining the increase in weight of the seminal vesicle and the ventral prostrate gland. By this method of evaluation norethandrolone is as anabolic as testosterone propionate, but it possesses only 6 per cent of the androgenic activity of the latter. Thus it is reported as having an androgenic-anabolic ratio of 1:16. The substance is active orally, does not possess any cortisone-like actions, and apparently is devoid of estrogenic effects. It does seem to have progesterone-like effects on the endometrium and has been reported as producing pituitary inhibition in experimental animals. The acute and chronic toxicity of norethandrolone is low.

As a protein anabolic agent norethandrolone has been introduced into therapy in the treatment of surgical traumatic conditions and disease states in which an increase in protein anabolism is desirable for hastening recovery. In preparation for, and recovery from surgery the agent may prove to be most useful. Norethandrolone has also been suggested in severe illness where the recovery may be assisted by an increase in protein anabolism, in the recovery phase of burn therapy, and in the nutritional care in wasting diseases such as carcinomatosis and tuberculosis.

The drug is available in 10-mg. tablets. The average adult dose is from 3 to 5 tablets daily. The dosage will vary according to the needs and the response of the patient. High doses of 100 mg. per day may elicit mild androgenic effects. The drug is contraindicated in cases of prostatic carcinoma. Nausea and edema may be side effects of norethandrolone therapy. The drug is discontinued if fluid retention is prominent in patients with a demonstrable or incipient circulatory or renal failure. Norethandrolone has produced jaundice and is suspected of causing an alteration of liver function. The drug should be promptly discontinued if liver function tests are not normal. In general, it is not considered wise to administer the drug for periods longer than 3 months. A second course of therapy may be reinstituted after a 1-month rest period. Androgens are contraindicated in patients with carcinoma of the prostate because these hormones will accelerate the neoplastic process.

The other anabolic agents that are subsequently described have the same general indications and precautions of therapy that are set forth for norethandrolone. Their advantages are all largely theoretical, and additional critical clinical evaluation studies are necessary to assess their proper role in therapy (Roth, 1963). Reference should be made to the chapter on the pharmacologic response of the reproductive system to the androgens (Chapter 49) for further details regarding the use of these drugs.

**Nandrolone phenproprionate (Durabolin).** Nandrolone is 19-nor $\Delta^4$-androstene-$17\beta$-ol-3-one-$\beta$-phenyl propionate. This is a parenteral anabolic steroid which is said to provide an increase in protein anabolism for 1 to 3 weeks after a single intramuscular or subcutaneous injection. The recommended dosage of nandrolone for adults is 25 mg., given by intramuscular or subcutaneous injection once weekly. Nandrolone has the same uses and contraindications as the other anabolic agents.

**Nandrolone decanoate injection (Deca-Durabolin)** is a long-acting form of the drug dissolved in sesame oil. It is injected intramuscularly. The average dosage for adults is 50 to 100 mg. every 3 to 4 weeks.

**Stanozolol (Winstrol).** Stanozolol is an orally active anabolic steroid. It is $17\beta$-hydroxy-$17\alpha$-methylandrostano-[3,2-c]-pyrazole. It appears to be 30 times more anabolic and ¼ as androgenic as methyltestosterone when administered orally to experimental animals. Parenterally, it is reported to be $\frac{1}{20}$ as anabolic and $\frac{1}{40}$ as androgenic as testosterone propionate. Stanozolol is used as an anabolic agent in a manner similar to the related compounds. It has the same contraindications and precautions as the other anabolic steroids.

The average adult dose is 2 mg. 3 times daily by mouth. No specific time limitations for therapy have been proposed for stanozolol, but it must be used in a manner similar to the other synthetic steroids.

**Oxymetholone (Adroyd, Anadrol).** This drug is 2-hydroxymethylene-17$\alpha$-methyldihydrotestosterone. It is active orally. It has the same uses and contraindications as the other anabolic agents.

The average dose of oxymetholone for adults is 7.5 to 15 mg. per day by mouth. The drug should not be given for longer than 6 weeks at a time.

**Methandrostenolone (Dianabol).** Methandrostenolone is $\Delta^1$-17$\alpha$-methyltestosterone. It is an orally active anabolic steroid. The indications for use of this drug, the contraindications, and the precautions to be observed are the same as those for the other anabolic agents.

The average dose for adults is 5 to 10 mg. daily. The drug should not be given continuously for periods longer than 6 weeks. Drug therapy may be resumed after a rest period of 2 to 4 weeks.

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